57

Acc.
26.9.78

ISSN 0006-8950

Brain

A Journal of Neurology

Volume 101 Part I March 1978

The Gate Control Theory of Pain Mechanisms. P. D. Wall 1

Some Frequency Response Characteristics of Parkinsonism on Pursuit Tracking. Kenneth Flowers 19

Lack of Prediction in the Motor Behaviour of Parkinsonism. Kenneth Flowers 35

Carcinomatous Neuromuscular Syndromes. Thomas Paul, B. C. Katiyar, Surendra Misra and G. C. Pant 53

A Study of the Visual Defect in Verbal Alexia–Simultanagnosia. David N. Levine and Ronald Calvanio 65

Mental Phenomena Evoked by Electrical Stimulation of the Human Hippocampal Formation and Amygdala. Eric Halgren, Richard D. Walter, Diana G. Cherlow and Paul H. Crandall 83

Trigeminal False Localizing Signs and their Causation. J. E. A. O'Connell .. 119

Focal Contralateral Myoclonus Produced by Inhibition of Gaba Action in the Caudate Nucleus of Rats. D. Tarsy, C. J. Pycock, B. S. Meldrum and C. D. Marsden 143

Word-comprehension and Word-retrieval in Patients with Localized Cerebral Lesions. A. K. Coughlan and Elizabeth K. Warrington 163

Notices of Recent Publications 187

OXFORD: AT THE CLARENDON PRESS

Edited by C. G. PHILLIPS
Deputy Editor R. A. HENSON
with the help of

J. HUME ADAMS R. W. GILLIATT M. VOGT
A. N. DAVISON E. C. HUTCHINSON L. WEISKRANTZ

Assistant Editor E. MACDOUGALL
Secretary and Treasurer J. M. NEWSOM DAVIS

All editorial correspondence, typescripts and books for review to be addressed to The Editor of *Brain*, Hertford College, Oxford, OX1 3BW

Directions to Authors upon the Preparation of Papers

PAPERS must be typewritten on one side of the paper only and double-spaced, and submitted in duplicate with two sets of figures In addition to the full title of the paper, authors should supply a 'running title' which will appear at the heads of the pages. *Brain* does not publish preliminary reports of work in progress only exceptionally does it publish detailed studies of a single case The typescript should be carefully and finally revised before submission to the Editor Clarity of style and brevity of expression are essential Before submitting a paper it is always valuable to obtain the comments of colleagues who are unfamiliar with the work We refer intending authors to the *Journal of Physiology*'s 'Suggestions to Authors' price 10p post-free from Cambridge University Press, Box 92, 200 Euston Road, London, NW1

The paper should be accompanied by a declaration in the following terms· 'The work reported in the attached paper entitled has not been, and is not intended to be, published anywhere except in *Brain* '

BIBLIOGRAPHIC REFERENCES should be limited to essential literature, they should be listed at the end of the paper in alphabetical order, and not numbered *In the case of a Journal* author's name, date of publication in brackets. are followed by the title of the paper, the name of the Journal *in full* and underlined for italics, the volume number and the first and last page numbers of the paper quoted, both in Arabic numerals. *In the case of a book·* author's name, date of publication in brackets, title of book underlined for italics, place of publication, publisher's name, chapter and page numbers in Arabic numerals Works by the same author should be given in chronological order, and if there be more than one in a year, they are marked *a*, *b*, *c*, etc.; when an author's name recurs a short line is used *In the text* numbered references are not used, but the author's name is followed by the appropriate year in brackets

ILLUSTRATIONS should, where possible, be line drawings in Indian ink on separate white boards, numbered, and with the author's name on the back Drawings and other illustrations should not exceed twice the size of the reproduction and thus lines must be thick enough to show up after reduction. This applies also to the lettering and numbering which the authors are asked to provide Legends should be on separate sheets and numbered Desired positions of tables and figures should be marked by writing instructions enclosed within lines and brackets, e g (*Table 3 near here*) or (*Fig 4 near here*)

Half-tone photographs must be kept to a minimum. Excellent photographs with clear contrast are essential, especially for the reproduction of electron micrographs Authors may be asked to contribute to their cost. There should be a bar on all micrographs giving magnification, e g. 1 μm.

Authors are asked not to reprint their papers, or to authorize others to do so, without first consulting the Oxford University Press (Academic Division), Walton Street, Oxford, OX2 6DP.

Fifty free offprints are sent to the authors, who may order more direct from Oxford University Press, Walton Street, Oxford, OX2 6DP when they get their proofs

Subscription rate for an annual volume of four issues £19.00 ($42) post free, or for subscribers resident in the U K £16 50. Single Issue. £5.00 ($12) net, postage extra

Please address correspondence on business matters as follows:

Subscriptions to the current volume. Subscriptions Department, Oxford University Press, Press Road, Neasden, London, NW10 0DD.

Orders and inquiries for back numbers Wm. Dawson & Sons Limited, Cannon House, Folkestone, Kent

Inquiries about advertising, offprints and copyright· Academic Division, Oxford University Press, Walton Street, Oxford, OX2 6DP

CP25684
COP-H-06642-57-P25684

Brain

A Journal of Neurology

Volume 101 Part I March 1978

The Gate Control Theory of Pain Mechanisms. P. D. Wall 1

Some Frequency Response Characteristics of Parkinsonism on Pursuit Tracking. Kenneth Flowers 19

Lack of Prediction in the Motor Behaviour of Parkinsonism. Kenneth Flowers 35

Carcinomatous Neuromuscular Syndromes. Thomas Paul, B. C. Katiyar, Surendra Misra and G. C. Pant 53

A Study of the Visual Defect in Verbal Alexia–Simultanagnosia. David N. Levine and Ronald Calvanio 65

Mental Phenomena Evoked by Electrical Stimulation of the Human Hippocampal Formation and Amygdala. Eric Halgren, Richard D. Walter, Diana G. Cherlow and Paul H. Crandall 83

Trigeminal False Localizing Signs and their Causation. J. E. A. O'Connell .. 119

Focal Contralateral Myoclonus Produced by Inhibition of Gaba Action in the Caudate Nucleus of Rats. D. Tarsy, C. J. Pycock, B. S. Meldrum and C. D. Marsden 143

Word-comprehension and Word-retrieval in Patients with Localized Cerebral Lesions. A. K. Coughlan and Elizabeth K. Warrington 163

Notices of Recent Publications 187

JOURNAL OF MENTAL DEFICIENCY RESEARCH

Editor: Dr B. W. Richards

THE JOURNAL OF MENTAL DEFICIENCY RESEARCH contains original research on medical and psychological problems relevant to mental subnormality.

Recent articles include:

The Recurrence of Mongolism in Sibships, B. W. Richards

Serum Cholinesterase (Pseudocholinesterase) in Down's Syndrome: 1. Phenotype Frequencies at the E_1 and E_2 Loci, Anne H. Drew and A. T. Rundle

The Use of the Vineland Social Maturity Scale, the Merrill-Palmer Scale of Mental Tests (Non-Verbal Items) and the Reynell Developmental Language Scales with Children in Contact with the Services for Severe Mental Retardation, Judith Gould

Chemical Analysis of an Angiofibroma from a Patient with Tuberous Sclerosis, M. H. Fischer, J. S. Fortune, S. H. Foster and B. H. Gilbert

The Ante-Natal Detection of Down's Syndrome: Some Demographic Aspects, D. P. Forster

Double Autosomal Trisomy: (48,XX,+18,+21): Case Report and Review of Literature, K.-P. Grosse and G. Schwantitz. **Appendix: Results of Dermatoglyphic Analysis,** Danuta Loesch

Interchromosomal Duplication for the Short Arm of Chromosome No. 9: Report of Three Cases Due to a Familial Translocation t(9;11) and One Case with a De Novo 47,XX,+9p Karyotype, C. C Lin, G. Holman, L. Sewell, P. Bowen and B. Bierderman. **Appendix: Results of Dermatoglyphic Analysis,** Danuta Loesch

Published quarterly by
THE NATIONAL SOCIETY FOR MENTALLY HANDICAPPED CHILDREN
Pembridge Hall, 17 Pembridge Square, London W2 4EP

Yearly Subscription £10.00 U.S.A. $30.00

Pitman Medical

MANAGEMENT OF NEUROLOGICAL DISORDERS

B ASHWORTH and M SAUNDERS

Many patients with neurological disorders are cared for in the community or in hospital and not dealt with in a specialised unit. In the past the treatment of these conditions was unrewarding and often regarded as an academic exercise. Recent developments in intensive care, rehabilitation and drug therapy have helped these patients.

Many challenges remain, but this book provides a guide to modern management. It is aimed primarily at medical practitioners, but will also be of interest to nurses, physiotherapists, and occupational therapists who work with these patients. The approach is practical and common problems are emphasised.

276 pages Cased £7.50 net

Brain

General Index

A re-issue of the first part of the General Index, covering Volumes 1—23 (1878—1900) and a recently compiled second part covering Volumes 24—48 (1901—1925) are now available to subscribers at £2·00 each, postage Part 1 (25p) Part 2 (20p) Parts 1 and 2 (40p). A third part (1926—1950) will follow.

Please write, enclosing money with order, to:
Wm Dawson and Sons Ltd.,
Back Issues Department,
Cannon House,
Folkstone, Kent CT19 5EE, England.

Back issues of BRAIN can also be obtained from Wm Dawson and Sons Limited, Please apply direct for prices and availability.

CHARLES C THOMAS • PUBLISHER

MEDICAL ASPECTS OF MENTAL RETARDATION (2nd Ed.) *edited by* **Charles H. Carter,** *Sunland Center, Orlando, Florida. (32 Contributors)* The completely revamped Second Edition of this volume offers a singularly useful overview of medical considerations in mental deficiency. The contributors examine and explain genetics and cytogenetics, infections, trauma, cranial abnormalities, poisons, nutrition, and prenatal and postnatal damage. Community diagnostic and treatment centers, cerebral metabolism, treatment with drugs, electroencephalography, neurocutaneous symptoms, degenerative brain conditions, metabolic disorders and many other closely related etiologies are also explored. *'78, 912 pp. (6 3/4 x 9 3/4), 436 il., 47 tables, $59.50*

DIAGNOSIS AND REHABILITATION IN CLINICAL NEUROPSYCHOLOGY *by* **Charles J. Golden,** *The Univ. of South Dakota, Vermillion, South Dakota.* This book offers a unique integration of the theoretical basis, experimental research, and clinical and diagnostic process of the emerging field of clinical neuropsychology. An initial discussion of the connection between brain structures and overt behavior prepares the reader for later, more detailed analyses. The main section focuses on clinical test procedures and on ways in which psychological testing can be used to identify a brain disorder, localize the area of a lesion, and determine underlying causes. A final section discusses factors in the recovery of a patient. *'77, 304 pp., 11 il., 13 tables, $14.75*

REFLEX TESTING METHODS FOR EVALUATING C.N.S. DEVELOPMENT (2nd Ed., 6th Ptg.) *by* **Mary R. Fiorentino,** *Newington Children's Hospital, Newington, Connecticut. Foreword by* **Burr H. Curtis.** This book is useful in the initial and periodic examination of all infants and children through six years of age. It will be of help in the diagnosis and evaluation of such patients where abnormal reflexive reactions are suspected. "This monograph will be of value to all who have occasion to deal with children with cerebral palsy."—*Archives of Neurology '77, 72 pp. (6 3/4 x 9 3/4), 78 il., 1 table, $8.50*

DECISION MAKING AND THE DEFECTIVE NEWBORN: Proceedings of a Conference on Spina Bifida and Ethics *edited by* **Chester A. Swinyard,** *Stanford Univ. School of Medicine, Palo Alto, California. Foreword by* **Robert E. Cooke.** *(49 Participants and Contributors)* Using spina bifida as a prototype defect for an interdisciplinary study, this book examines the medical, ethical, theological, social and legal aspects of selective passive euthanasia. While no final resolution of the problem is offered, the book makes a great contribution to an understanding of the situation by raising and debating issues, by indicating differences in medical opinion and by bringing currently ongoing practices out into the open. *'77, 672 pp., 19 il., 29 tables, $24.75*

REFLEX EPILEPSY, BEHAVIORAL THERAPY AND CONDITIONAL REFLEXES *by* **Francis M. Forster,** *Univ. of Wisconsin, Madison, Wisconsin.* The first portion of this singularly comprehensive text is concerned with the various causes of reflex epilepsy, such as visual and auditory stimuli, higher cognitive functions, somatosensory stimulation, and eating and movement. Each of these causes is examined closely in a separate chapter. The latter half of the text considers classification and differential diagnosis of reflex epilepsy, and the methods, principles of application, maintenance or reinforcement, selection of cases, role of medication, and results of behavior therapy in the treatment of the disorder. *'77, 328 pp., 87 il., 22 tables, $22.75*

NEUROLOGY OF THE OCULAR MUSCLES (2nd Ed., 8th Ptg.) *by* **David G. Cogan,** *Harvard Medical School, Boston, Massachusetts.* The correlation of clinical disturbances with the physiology and anatomy of the centers and tracts that control the nervous mechanisms of the eye is exceptionally well done. The manual includes nearly all that is known of the anatomy and physiology of those centers and tracts, and the known signs and syndromes resulting from lesions in them. Every conclusion is documented either by personal experience or by experiments and thorough review of literature. *'77, 320 pp., 169 il. (3 in color), $13.75*

Orders with remittance sent by air, postpaid

301-327 East Lawrence Avenue • Springfield • Illinois • 62717 • USA

Brain (1978), **101**, 1-18

THE GATE CONTROL THEORY OF PAIN MECHANISMS

A RE-EXAMINATION AND RE-STATEMENT

by P. D. WALL

(From the Cerebral Functions Research Group, Anatomy Department, University College London, Gower Street, London, WC1E 6BT)

INTRODUCTION

IN 1965, Melzack and I proposed a gate control theory and later we modified and modernized the original proposal (Melzack, 1973; Wall, 1973, 1974, 1976). Nathan (1976) has written a detailed review in which he concentrates particularly on mechanisms. Here I would like to extend his review to show where new knowledge requires a modification of our previous thinking, where the theory stands now and where gaps in our knowledge still prevent movement from speculation to reality. There were certain points in our original statement which seem to have been misunderstood and these need clarification. The diagram of mechanism we published had all the disadvantages of excessive clarity with its emphasis on the substantia gelatinosa and presynaptic mechanisms. The body of the paper mentioned other possible mechanisms but it has seemed to some that the entire theory rested on the diagrammatic mechanism which we shall see is not the case. Of course there have been many interesting discoveries since 1965 which need reviewing. Some of these new facts show that the data on which some of the theory was based was frankly misleading. Finally we shall try to show where the persistent inadequacy of technique still prevents an elucidation of mechanism.

Specificity

Nathan writes 'The theory neglected the facts known about stimulus-specificity of nerve fibres'. There are two completely different uses of the word specificity; one diagnostic and the other prognostic. The diagnostic meaning is that one can specifically diagnose the nature of the events which occur at a peripheral receptor which generates nerve impulses. All investigations of peripheral nerve fibres have shown that under defined conditions there is a fixed and specific relation between stimulus and response. Any theory which neglects these facts should indeed be dismissed. The general paper which Melzack and I wrote in 1962 and the more detailed one in 1965 started from the fact of stimulus-response specificity in this diagnostic sense. It is true, of course, that preceding stimuli and concomitant events modify the excitability of a nerve terminal and that nerves respond to adequate changes of both mechanical, thermal and chemical perturbations of their environment but these addenda do not deny the basic specificity of the stimulus-response connection under defined conditions. However, we do take very strong issue with the use of the term specificity in its predictive prognostic sense. This version states that if a nerve impulse is detected in a particular type of nerve fibre, then one can make a specific prediction of the type of sensation which will result. The diagnostic use of the word refers to the past cause of the observed nerve impulse and we accept this as fitting the overwhelming body of facts. The predictive use of the word states what will happen in the future as a consequence of the impulses. Far from neglecting the second use of the word specificity the major point of both our papers (1962, 1965) was that we denied that the facts allowed one to move from the observations of impulses in some special fraction of peripheral fibres to a prediction that a specific sensation would inevitably result. In insisting on this differentiation, we were not being particularly revolutionary. The introduction of the word 'nocicipient' by Sherrington (1903) was an example of a diagnostic word: a structure detecting the existence of a noxious event is a nociceptor. The discovery of a nociceptor does not allow a *volte face* to label the fibre a 'pain' fibre which presumes an ability to predict the consequences of excitation of nociceptors. The use of the word 'specific' in its diagnostic sense frees one to classify nerve fibres in many more ways than is possible if a classification is attempted where each category of fibre must be associated with a modality of sensation.

Pain

Our research and thinking was prompted by the problems of pain and its wild and variable relation to the stimulus which evokes it. We then tried to propose ways in which this psychological phenomenon could be related to the rigid stimulus bound response properties of peripheral nerve. It is true that in exactly defined experimental situations, the trained subject can relate perceived pain strength to stimulus intensity but even amongst trained subjects a comparison of studies shows a wide variation of the relationship reported in different laboratories (Sternbach and Tursky, 1964). In the real world outside the laboratory, the variation of the relationship between pain and injury occupies all positions between injury with no pain and pain with no injury. These variations are not to be dismissed as vagaries of the mind and they are therefore a proper study for science and neurology. Not only does the subjective statement vary but the objective signs of reflex activity and autonomic responses are equally and independently variable. Some variation follows known rules. Injury is followed by tenderness. Some tenderness, primary hyperæsthesia, is to be explained by the sensitization of previously high threshold endings by tissue breakdown of products so that light pressure evokes impulses in fibres which previously required intense pressure for excitation. Such a change in characteristics of stimulus response requires no modification of classical theory. However, if primary hyperæsthesia persists, a secondary tenderness spreads to areas far distant from the injury. The most dramatic examples occur in referred pain where normal skin becomes tender indicating some deep and distant disorder. Here innocuous stimuli to normal tissue evoke pain. Any theory of pain must take such pain into account. Similarly the neuropathies, some painful, some painless, must be accounted for. In 1965 we attempted to consider all types of pain and their variations and to suggest a way in which the facts then known about physiology and anatomy might be brought together to produce a correct framework for pain mechanisms. We broke out of the straight-jacket of classical theory only to find ourselves still in a mad-house. To help understand the present position, I would like first to make a general re-statement of the gate control theory in a form which I think is useful and defensible and then to discuss the details in which we were clearly wrong in the light of subsequent work and the details which remain unknown.

Gate Control Theory: a General Re-statement

(1) Information about the presence of injury is transmitted to the central nervous system by peripheral nerves. Certain small diameter fibres (Aδ and C) respond only to injury while others with lower thresholds increase their discharge frequency if the stimulus reaches noxious levels.

(2) Cells in the spinal cord or fifth nerve nucleus which are excited by these injury signals are also facilitated or inhibited by other peripheral nerve fibres which carry information about innocuous events.

(3) Descending control systems originating in the brain modulate the excitability of the cells which transmit information about injury.

Therefore the brain receives messages about injury by way of a gate controlled system which is influenced by (1) injury signals, (2) other types of afferent impulse and (3) descending control.

Peripheral Nerves

Normal. In 1965, the literature on mammalian nociceptors was wrong and highly misleading because it appeared that adequate investigations of all types of peripheral nerve fibres had been carried out. In the entire literature, only 20 myelinated fibres which could be called nociceptors had been described. The most complete study by Hunt and McIntyre (1960) found 7 nociceptors among 421 A fibres. This careful paper showed that their distribution of observed conduction velocities matched the observed distribution of fibre diameters and therefore it seemed that they had adequately sampled the entire A population. Of the unmyelinated C fibres, Iggo had reported a few nociceptors (1960). It seemed possible, however, that these might have been damaged by his dissection method because Douglas and Ritchie (1957) with their non-intrusive collision technique reported that all C fibres responded to low intensity stimuli. We reasonably concluded 'These data suggest that a small number of specialized fibres may exist that respond only to intense stimulation' (Melzack and Wall, 1965). We knew of course from the extensive work from Adrian (1931) and Zotterman (1939) and Collins, Nulsen and Randt (1960) that it had been repeatedly shown that stimulation of smaller diameter A and C fibres evoked pain and we had to match this fact with the apparent rarity of pure nociceptors. The suggested solution was that an important part of the injury signal was the high frequency and massed firing of those fibres which had a wide dynamic range and responded to low level stimuli and then increased their discharge rate with more intense stimuli. These wide dynamic range fibres also cluster in the smaller diameter range. Electrical stimuli which excited such fibres would then deliver a false injury signal because of the combined spatial and temporal summation of the impulses on central cells.

The facts were wrong. The dissection and recording techniques had grossly biased the sampling in favour of larger fibres. We now know, thanks largely to the single fibre recordings in animals of Iggo, and Perl and Burgess, that substantial numbers of nociceptors exist (reviewed in Iggo, 1973). The micro-electrode technique of Vallbo and Hagbarth shows that these fibres also exist in man (Torebjork and Hallin, 1973, 1974; Van Hees and Gybels, 1972). Some of these nociceptors become sensitized by prolonged or repeated noxious stimulation so that their threshold drops and they are excited by normally innocuous stimuli (Bessou and Perl, 1969) an observation which may be related to the primary hyperalgesia. The sensitization of nociceptors does not exclude them from being useful in signalling the presence of damage since their receptors can be said to sense the continuing subliminal presence of injury which then reaches threshold when minor innocuous stimuli occur. Some terminals become less sensitive following injury and these clearly do not signal the sequelæ of injury or contribute to the pain suffered at some time after injury. The discovery of the class of nociceptive fibres is of obvious importance but as we stated (1965) 'this does not mean that they are "pain fibres" in that they must always produce pain and only pain when they are stimulated'. Nor does it mean that the high frequency discharge of low threshold fibres of wide dynamic range can now be neglected as playing no role in conveying to the CNS part of the message that injury exists.

Pathological peripheral fibres. The 1965 paper was written before the present explosion of information about the anatomical state of nerves in the peripheral neuropathies. We were highly influenced by the one detailed study available, on post-herpetic neuralgia (Noordenbos, 1959) in which Weddell had shown that intercostal nerve biopsy specimens provided by Noordenbos had a preferential loss of large myelinated fibres and Noordenbos had generalized from this observation to propose that the pain was a consequence of a loss of inhibition normally provided by the large fibres. We now know that loss of large fibres is not necessarily followed by pain. In Friedreich's ataxia (Dyck, Lambert and Nichols, 1971) there is just such a preferential large fibre deficit without pain. I thought it might still be possible to defend the generalization for adults since Friedreich's ataxia begins at a very early age and it is possible that spinal cord compensations occur during the development of the unusual afferent pattern. This is no longer tenable, however, since Thomas (1975) showed that the polyneuropathy of renal failure in adults is not associated with complaints of pain although there is preferential destruction of large fibres. Any attempt to correlate the remaining fibre diameter spectrum with the symptomatology of neuropathies is no longer possible as is apparent in recent reviews (Dyck, Thomas and Lambert, 1974; Thomas, 1975). All combinations have been reported. For example, Fabry's disease is associated with loss of small myelinated fibres and pain (Kocen and Thomas, 1970) but one hereditary sensory neuropathy (Schoene, Asbury, Astrom and Masters, 1970) is associated with a loss of myelinated fibres, preserved C fibres and analgesia. In an attempt to make sense of this chaos, Dyck, Lambert and O'Brien (1976) introduced the dynamic factor of the presence of ongoing degeneration as well as the static existence of some particular fibre spectrum at the time of biopsy. Of their 72 patients with peripheral neuropathy, pain was present in 19 of 25 patients with acute fibre degeneration and only in 5 of 34 patients with other types of degeneration. Their conclusion is less impressive when one notices that 12 of the 19 patients with pain and acute degeneration had only 'a slight degree of pain, not a chief complaint and analgesics were not used'. However, it does seem reasonable to conclude that fibre diameter alone is not enough or is completely irrelevant to explain the origin of pain in the neuropathies. How can this be? One possible answer is that the biopsy has not sampled the relevant region of nerve. In a case of tabes dorsalis, the peripheral fibre spectrum was normal in spite of complaints of pain (Dyck, Lambert and Nichols, 1971), and one may presume that in this case the disorder was central to the dorsal root ganglion. In experimental neuromas of the sciatic nerve of the rat, the fibre spectrum of the parent sciatic nerve fibre is almost normal but the small myelinated afferents and the unmyelinated afferents conduct impulses from the neuroma (Devor and Wall, 1978). An anatomical study of the neuroma does not permit a statement of the diameter of the parent fibres which give rise to conducting fine sprouts which make up the neuroma. This leads to a further problem in interpreting a biopsy spectrum since one cannot know that an observed fine fibre is not connected to a larger fibre or what are the central connections of the observed fibre or what are the properties of its peripheral receptor. Obviously anatomy does not predict physiology. Intact fibres may be completely or partially blocked. Furthermore, as implied by Dyck *et al.* (1976), degenerating fibres may become spontaneously active or easily excited. Diamond (1959) showed that regenerating fibres become sensitive to acetylcholine. Wall and Gutnick (1974*a*, *b*) showed that fibre sprouts within a neuroma are spontaneously active, sensitive to pressure, silenced by repetitive antidromic invasion and sensitive to noradrenaline. Evidently degenerating, sprouting and regenerating fibres have unusual impulse generation and conduction properties. It might be thought that recording from single fibres in patients with neuropathies would resolve these issues but this is not entirely true because, like the biopsy, only one area is observed and the central destination of an observed impulse is not known. It is evident that we are unfortunately almost as free to speculate about the cause of pain in neuropathies now as we were in 1965 because the cause is unknown.

Cord Cells Responding to Injury

Since only a partial survey of spinal cord cells had been carried out by 1965, we postulated the existence of injury detecting cells and gave them the non-committal name of T cells. Now that many more cells have been recorded, one must first ask what are the criteria by which cells will be labelled as being concerned with pain mechanisms. Those committed to specificity theory consider only cells responding to injury and to no other stimuli. I take a more conservative approach and consider all cells responding monosynaptically to nociceptive afferents. Some would require that candidate cells must send axons into the contralateral ventral white matter. This is an unrealistic requirement since peripherally evoked pain recurs some weeks or months after anterolateral cordotomies. Some would even require that the cells must project to the thalamus, an even more unrealistic requirement in view of the generally unsatisfactory results of thalamotomies for the long-term treatment of pain (White and Sweet, 1969). It is not even necessary that the cells should project into long running pathways since it has been known since Schiff that bilateral and polysynaptic pathways can mediate pain (Basbaum, 1973). It would be ideal if one could correlate the firing of cells with behaviour evoked by strong stimuli to determine the necessary if not sufficient conditions for the evocation of pain but no such experiments are available. Similarly, no chemical or surgical blockade succeeds in permanent abolition of pain unless a complete disruption of projection pathways is achieved. Therefore these manœuvres do not yet provide experimental evidence for selecting which cells or axons are crucial. A novel method introduced by Mayer, Price and Becker (1975) in which stimulus parameters needed to evoke pain and to stimulate particular types of cells are compared, offers a way of identifying cells involved in pain. What are the candidate cells?

Marginal cells, lamina 1. Cells exist in this lamina which respond only to nociceptive afferents and to no others (Christensen and Perl, 1970). Some of these project into contralateral ventral white matter and some of these even as far as the thalamus (Dilly, Wall and Webster, 1968; Trevino, Coulter and Willis, 1973; Kumazawa, Perl, Burgess and Whitehorn, 1975). One must warn that such cells have been detected by these skilled and hard workers in very small numbers; an average of only two cells responding specifically to a nociceptive input have been recorded from each experimental animal. It would seem premature to adopt these cells as all that is necessary to explain pain mechanisms as Kerr (1975) has done. They exist in a population of cells most of which receive convergences from many types of peripheral afferent (Wall, 1968). This fact warns that one should be cautious in attributing one and only one function to a particular cell since, as we shall see, the degree of convergence is under control of other afferents and descending systems and is also dependent on the activity of segmental interneurons. Furthermore, these cells do not match a number of simple expected correlations between their firing and pain behaviour. A powerful substance such as bradykinin does not excite them and their discharge is not prolonged following injury (Christensen and Perl, 1970).

Lamina 5 cells. There are large numbers of cells in lamina 5 which respond to both myelinated and unmyelinated nociceptive afferents (Wall, 1967). They respond to injury and to algesic substances (Besson, Conseiller, Hamann and Maillard, 1972). Their response to injury is decreased in the presence of narcotics and anæsthetics (reviewed by Mayer and Price, 1976). Some have cutaneous receptive fields, while some receive high threshold afferents from muscle and others from viscera (Pomeranz, Wall and Weber, 1968). In addition to their response to nociceptive afferents, most of these cells also respond to low threshold afferents. Their receptive fields are therefore complex (Hillman and Wall, 1969). The most dramatic of these convergences of high and low threshold afferents are on those cells which respond to high threshold visceral afferents and also to low threshold afferents from skin (Pomeranz *et al.*, 1968). The existence of these low threshold excitatory convergences exclude these cells as candidates if complete specificity is required, but includes them if one wishes to explain such phenomena as hyperæsthesia where light stimuli increase pain. Some of these cells project to opposite ventral white matter and some to thalamus (Trevino *et al.*, 1973). The papers of Mayer, Price and Becker (1975) and Price and Mayer (1975) show that cells of this type are strong candidates for playing a role in pain evoked by stimulation of the ventro-lateral cord in man.

Other cells. A system of cells responding to intense peripheral stimulation and conducting slowly along the core of the spinal cord, medulla and mid-brain was described by Collins and Randt (1960); no single unit recordings have yet been made. It must be warned that recording methods still do not allow an exhaustive sampling of spinal cord cells. Therefore it may be that crucial populations of small cells remain undetected. One obvious group of small cells which have until very recently resisted recording are those in substantia gelatinosa. Heimer and Wall (1968) showed that fine afferents terminate on these cells in cat and rat. Kumazawa and Perl (1977) have shown that cells in this region in monkey respond to nociceptive C afferents. Our own unpublished work on cat shows that there are several types of cells in substantia gelatinosa, many of which respond to low threshold afferents. The anatomy of the region shows that cells only project over very short distances (Szentagothai, 1964). Therefore they might only play a local segmental role in modulating the transmission of impulses from arriving afferents to cells which project over long distances (Wall, 1962). However, it is also possible that they play a role in pain mechanisms as a system of multiple chains of short projection cells as suggested by Noordenbos (1959). A continuous column of spinal grey matter is not essential for the perception of pain since cases of syringomyelia have been seen with complete obliteration of some segments of grey matter but preservation of white matter and of pain sensation. It is quite possible, however, that short loops of axons extend from grey to white to grey matter and thereby bypass the interrupted continuous column of grey matter in such cases.

Do Peripheral Afferents Inhibit the Cells Excited by Nociceptive Afferents?

An essential feature of our hypothesis was that cells excited by injury afferents would be inhibited by low threshold afferents. Subsequent discoveries have fully supported this aspect of the theory. Cervero, Iggo and Ogawa (1976) show that the discharge of the lamina 1 cells which are excited by noxious heating or by electrical stimulation of the A delta and C cutaneous afferents are inhibited by electrical stimulation of the large (Group 2) cutaneous myelinated afferents. An essential feature of the organization of lamina 5 cells is that they possess an inhibitory surround receptive field which is activated by low threshold afferents (Hillman and Wall, 1969). From the excitatory centre of the receptive field, low threshold afferents evoke an excitation followed by a prolonged period of inhibition. Since the low threshold large diameter myelinated afferents send collaterals rostrally in the dorsal columns, it is not surprising that dorsal column stimulation also inhibits lamina 5 cells (Hillman and Wall, 1969). Foreman, Beall, Applebaum, Coulter and Willis (1976) show that this inhibition is produced in the response of spinothalamic tract neurons in primates by stimulation of the dorsal columns. Electrical stimulation of bundles of axons is, of course, a crude often misleading manœuvre; since it bypasses the specificity of input from different terminals, it fails to initiate the natural temporal pattern of impulses and it smears the differing effects which depend on the spatial origin of the fibres. In spite of this crudity, electrical stimulation of peripheral nerves or dorsal columns partially imitates the inhibition of lamina 5 cells which can be produced by discrete light pressure stimuli in spatially specific parts of the cells' receptive fields. All the candidate cells which respond to injury and which have been tested for their response to low threshold afferents have been shown to be inhibited.

What is the Mechanism of the Afferent Inhibition?

Melzack and I (1965) proposed as a secondary hypothesis that the gate control might be operated by a pre-synaptic mechanism but we also stated that postsynaptic mechanisms could also operate. In the diagram we made the error, for the sake of simplicity, of showing only a pre-synaptic mechanism and a number of critics including Nathan have missed what was written in the text and have assumed that we proposed only a pre-synaptic mechanism and furthermore that the whole theory rested on this mechanism. The theory in fact rests on the presence of inhibitions and facilitations and these are undoubted. The question of whether these are pre- or post-synaptic is secondary but, of course, of considerable interest. Hongo, Jankowska and Lundberg (1968) showed that there were undoubted signs of post-synaptic inhibition and this work remains the only definite identified location of an inhibition. This does not exclude the possibility that pre-synaptic inhibition might not also operate. It is certain that there are depolarizations of the terminals of the afferent fibres. These generate the dorsal root potentials and the lowering of threshold of the afferent fibre's terminals. The mechanism by which this afferent depolarization occurs remains in doubt. The depolarization is very loosely coupled with an inhibition of transmission from afferents to interneurons. We had suggested that these pre-synaptic changes were associated with a block of transmission from the entering fibres into the terminal arborization (Howland, Wall, Lettvin, McCulloch and Pitts, 1955) and Eccles (1964) had proposed that a depolarization of terminals would result in a decrease of transmitter release. Both of these suggestions are based on circumstantial evidence and still lack proof in the mammal. Neither of these proposals excluded that there was not a concomitant and perhaps predominant post-synaptic change which explained the observed inhibition. I wish to emphasize that an undoubted pre-synaptic depolarization occurs; its origin is unknown; it roughly coincides with an inhibition; however, for the only candidate cells which have been examined, there are also post-synaptic changes. Therefore, it is still a matter of speculation to propose the origin of the observed inhibition. Unlike some invertebrate synapses, the mammalian dorsal horn still contains synaptic interconnections too small and too intricately interwoven to allow definite causal mechanisms to be demonstrated which explain observed input-output functions.

It was proposed that the cells of substantia gelatinosa played a role in the modulation of transmission. Their anatomical location with short running axons interposed in the junction region of afferents and dendrites made them suitable for this role. Further details of this anatomy (Kerr, 1975) emphasize this possibility but do not help in the pre- or post-synaptic controversy. A positive physiological reason for their inclusion was the observation that the Lissauer tract which interconnects the cells of substantia gelatinosa was capable of spreading the primary afferent terminal depolarization from one segment to another (Wall, 1962). Since that time Denny-Brown, Kirk and Yanagisawa (1973) have given more substantial reasons for involving the Lissauer tract and therefore the substantia gelatinosa in the regulation of the effectiveness of afferent impulses. They showed that the dermatome subserved by an isolated dorsal root, as tested by behavioural reaction to cutaneous stimulation, was greatly expanded if the Lissauer tract, entering the innervated segment, was sectioned. Exciting and important as this observation is, it must be pointed out that it cannot tell how the substantia gelatinosa cells are involved in the pathway from the dorsal root to the observed motor responses. It is clear that techniques will have to be developed to modify independently the action of substantia gelatinosa cells and to record from them before proceeding to test how they are involved in the excitability of reflex areas or sensory transmission. All the work since 1965 shows that cord cells responding to injury are subject to inhibitions of peripheral origin but the mechanism remains obscure.

Facilitations

There has been remarkably little progress on the subject of facilitation as distinct from excitation. The reason is a technical one. The cells under discussion are excited by small diameter afferents which conduct slowly and the action potentials in the fibres are difficult to record. In certain favourable situations, cells may respond only to a particular group of small afferents as in the case of lamina 5 cells responding to the splanchnic nerve (Pomeranz *et al.*, 1968) or the lamina 1 cells (Christensen and Perl, 1970). This allows a satisfactory timing of the first discharge of the cell and a proof that it is responding, probably monosynaptically, to the leading edge of the arriving slow volley; but many of these cells then respond repetitively and it is not easy to prove if these subsequent responses of the cell are due to excitation by trailing slowly conducted impulses in the afferent volley or are produced by some reverberation within the cell or by the action of some nearby cells. We proposed in 1965 that a source of long lasting facilitation was a hyperpolarization of the terminals of afferent fibres produced by the arrival of volleys in small diameter afferents. There was, for a time, a controversy as to whether this primary afferent hyperpolarization existed at all but it now seems generally agreed that hyperpolarizations exist but are not necessarily associated with the arrival of afferent volleys in small nociceptive afferents (reviewed by Wall, 1973). In earlier work (Wall, 1959) I gave reasons to suggest that the prolonged repetitive firing of dorsal horn interneurons was neither a property of the afferent volley nor of the responding transmitting cells and therefore must be attributed to some other mechanism. For the reasons stated, this problem has not been a major target of investigation although it will be important in understanding pain mechanisms particularly in those situations of hypæsthesia where slowly repeated stimuli result in a slow wind up of sensation reminiscent of the wind up of cell response (Mendell, 1966). These gradually increasing pains are evoked by such slowly repeated stimuli that each stimulus must leave behind it a period of facilitation which exaggerates the effect of the subsequent stimulus (Noordenbos, 1959) and cannot be explained by a dispersion of the arrival time of the afferent volley.

Are the Injury Detecting Cord Cells Subject to Descending Control?

An essential feature of the gate control hypothesis was that the cord cells which received nociceptive afferents would be under descending control and this has proved to be the case in all cells so far examined. In the decerebrate animal, a powerful tonically active inhibitory system within the pons and medulla projects into the dorsal horn. This system inhibits the effects of cutaneous and visceral afferents on dorsal horn neurons. This was first noticed by Sherrington and Sowton (1915) in comparing reflex activity in spinal and decerebrate animals. Wall (1967) showed that it was possible to follow the activity of single cells before, during and after the cold block of a segment of spinal cord which blocked the descending inhibition in cerebrate animals. Cervero *et al.* (1976) located 46 cells in the marginal layer, lamina 1, 35 of which responded only to nociceptive afferents and 11 responded to sensitive mechanoreceptors as well as to nociceptors. When the spinal cord was cold blocked, both types of cell became more excitable. The lamina 5 cells have been studied in more detail by Wall (1967) and Hillman and Wall (1969). In the decerebrate state, their receptive fields are smaller, the ongoing activity is less, the inhibitory areas are more effective and the response to injury is smaller than in the spinal state. Small lesions and micro-electrode stimulation show that this inhibitory pathway descends in the dorsolateral white matter. Other descending systems such as the pyramidal tract (Fetz, 1968) and vestibulospinal system (Erulkar, Sprague, Whitsel, Dogan and Janetta, 1966) also control dorsal horn interneurons. One of these systems descends indirectly from the periaqueductal grey matter of the mid-brain, PAG. Stimulation of this area produces a profound analgesia in animals and man (Reynolds, 1969; Mayer and Liebeskind, 1974; Adams, 1976). The same stimulation inhibits the response of lamina 5 cells to noxious stimuli (Oliveras, Radjemi, Guilbaud and Liebeskind, 1974). The behavioural analgesia must be produced by a descending inhibitory system since unilateral section of the dorsolateral white matter in rat thoracic cord abolishes the analgesia in the ipsilateral hind leg while leaving the other three limbs analgesic (Basbaum, Clanton and Fields, 1976; Basbaum, Marley and O'Keefe, 1976). The descending pathway seems to relay in the cells of the nucleus raphe magnus (Fields, Basbaum, Clanton and Anderson, 1977; Basbaum, Clanton and Fields, 1976) and to be dependent on monoaminergic transmitters (Engberg, Lundberg and Ryall, 1968; Akil and Liebeskind, 1975).

The Effect of the Success of Transcutaneous Nerve Stimulation on the Gate Control Theory

The most obvious prediction of the gate control theory was that stimulation of large diameter peripheral nerve fibres should raise the threshold for detecting injury in the region served by the stimulated nerve. Wall and Sweet (1967) immediately proceeded to test this with considerable trepidation since we did not know if the predicted threshold rise would be significant or, worse, if the excitatory effects in man would overwhelm the inhibitory ones. We were well aware of the fact that electrical stimulation of peripheral nerve produces an abnormal concatenation of spatial and temporal convergences of peripheral afferents on to central cells. However, we hoped that the artificial barrage produced by low level peripheral nerve stimulation would have an overall inhibitory effect on human cord cells as it does in the cat. The predicted rise of threshold was shown to occur in normal subjects (Higgins, Tursky and Schwartz, 1971; Satron and Goldstein, 1973; Campbell and Taub, 1973). In certain patients with chronic intractable pain, the effect of transcutaneous electrical stimulation is sufficiently powerful for therapeutic use. In a series of 336 cases with peripheral disease reported by Long and Hagfors (1975), 129 gained full relief of pain from counterstimulation while of 60 cases with central disorders only 2 responded. In a survey of over 3000 patients at various centres, 25 to 30 per cent of patients previously completely incapacitated by chronic pain were more or less completely relieved of pain (Long and Hagfors, 1975). Eleven of 30 chronic severe cases of post-herpetic neuralgia responded satisfactorily over long periods of time to transcutaneous stimulation (Nathan and Wall, 1974).

The theory proposed that stimulation of large diameter afferents would, on average, raise the threshold of central cells by increasing inhibition. In spite of the apparent support given to this proposal by the clinical results, I was from the beginning cautious about this conclusion for two reasons. One was the observation that certain types of pathological pain would completely disappear while leaving the area normally sensitive to pin prick and pinch (Lindblom and Meyerson, 1975). This suggested that there was something special about these pains whose control did not necessarily interact with 'normal' pain. The second reason was that some patients experience relief for hours after minutes of stimulation while the inhibitions which we observed in animals only outlasted the stimulus for seconds.

Campbell and Taub (1973) proposed that the electrical stimulation was so intense that the peripheral nerves themselves were blocked. Using pulse widths ten times those normally used and voltages five times higher, they presented possible evidence that peripheral nerves were blocked. Ignelzi and Nyquist (1976) also show peripheral nerve block in animals but they appear to have applied the full current across the sural nerve which is normally distributed across an entire leg. It has been known since the first man recovered from a bolt of lightning that intense electrical stimulation will block a nerve but can this be the explanation for the clinical results? The answer is no because if it were so the treated area should be anæsthetic, which it is not, and dorsal column stimulation should never work, although it does. Furthermore, in order to block a nerve with the intense currents used by Campbell and Taub, it is necessary to stimulate both large and small fibres before they block and even when part of the nerve is blocked the stimulation continues on the edge of the block. If only peripheral block were to occur the subject would be in intense pain during the onset of the block and while it was maintained. Since he is not, one must propose that some central inhibitory mechanism has been set off by the initial low stimulus intensities used and that this inhibition is sufficient to allow the subject to tolerate the subsequent barrage generated by the higher currents.

Worried by the discrepancy between the clinical results and our predictions in which the clinical relief over-fulfilled the prediction, Wall and Gutnick (1974*a*, *b*) turned to examine the physiology of abnormal peripheral nerve. In rats, the sciatic nerve was cut and the end was placed in a tube so that the neuroma developed within the tube. Impulses were recorded in single dorsal root fibres whose ends lay within the neuroma. The intact parent fibres which sprout to form the neuroma include many small diameter fibres (Devor and Wall, 1978). Many of these fibre terminals give rise to ongoing activity. We placed stimulating electrodes on the proximal intact nerve and, in imitation of therapeutic counter-stimulation, a 100 Hz 0·1 ms square wave stimulation was applied. To our surprise, the antidromic invasion of the sensory terminals in the neuroma by the high frequency train of impulses was followed by long periods of silence of the previous ongoing activity and by long periods of insensitivity to electrical or mechanical stimuli. After a few seconds of tetanus, these neuroma terminals took minutes or hours to recover their previous sensitivity. If normal intact terminals are invaded by such volleys they recover their excitability within seconds. It is evident that either the nerve impulse generator mechanism or the transmission properties of axons in a neuroma have abnormal properties which fail to recover after high frequency driving. If these abnormal properties exist in the membrane of human pathological peripheral axons, it may then be that part of the explanation for the effectiveness of electrical stimulation lies in the periphery rather than in the cord. One must stress, however, that it is still necessary to postulate central inhibition as well as a possible peripheral mechanism since otherwise it would be impossible to reach the required voltages of stimulation without inflicting intolerable pain. If the stimulating current is gradually raised during the application of surface stimulation with 100 Hz 0·1 ms square waves, a voltage is reached at which the subject feels a strong buzzing tingling sensation. If a short burst of stimuli at this voltage is applied without preconditioning, the result is intense pain. The reason for this difference is that the preceding low level stimuli have produced central inhibition. The striking and long lasting abolition of pain from damaged nerve by counter-stimulation may therefore be due to a combination of central inhibition and peripheral inactivation, but it remains possible that such nerves generate unusual central patterns of response which are particularly easily inhibited by afferents.

SUMMARY AND CONCLUSIONS

In 1965, we proposed that the transmission of information about injury from the periphery to the first central cells was under control. The setting of this control or gate was influenced by peripheral afferents, other than those which signalled injury. The gate was also influenced by impulses descending from the brain.

Subsequent work has fully supported and enlarged this view. All the cells so far discovered which transmit information from nociceptors are inhibited by low threshold afferents and by descending controls. The mechanism by which this control is achieved remains completely unknown. Pre-synaptic inhibition as a phenomenon isolated from post-synaptic inhibition is in doubt. Whether the inhibitions and facilitations are pre-synaptic or post-synaptic or both is unknown. The role of the substantia gelatinosa in any function is unknown. That a gate control exists is no longer open to doubt but its functional role and its detailed mechanism remain open for speculation and for experiment.

REFERENCES

ADAMS, J. E. (1976) Naloxone reversal of analgesia produced by brain stimulation in man. *Pain*, **2**, 161–166.

ADRIAN, E. D. (1931) The messages in sensory nerve fibres and their interpretation. *Proceedings of the Royal Society, B*, **109**, 1–18.

AKIL, H. and LIEBESKIND, J. C. (1975) Monoaminergic mechanisms of stimulation produced analgesia. *Brain Research, Amsterdam*, **94**, 279–296.

BASBAUM, A. I. (1973) Conduction of the effects of noxious stimulation by short-fibre multisynaptic system in the spinal cord of the rat. *Experimental Neurology*, **40**, 699–716.

—— CLANTON, C. H. and FIELDS, H. L. (1976) Opiate and stimulus-produced analgesia: functional anatomy of a medullo-spinal pathway. *Proceedings of the National Academy of Sciences*, **73**, 4685–4688.

—— MARLEY, N. and O'KEEFE, J. (1976) Effects of spinal cord lesions on the analgesic properties of electrical brain stimulation. In: *Advances in Pain Research and Therapy*. Edited by J. J. Bonica. New York: Raven Press, vol. 1.

BESSON, J. M., CONSEILLER, C., HAMANN, K. F. and MAILLARD, M. C. (1972) Modifications of dorsal horn cell activities in the spinal cord after intra-arterial injection of bradykinin. *Journal of Physiology*, **221**, 189–205.

BESSOU, P. and PERL, E. R. (1969) Response of cutaneous sensory units with unmyelinated fibres to noxious stimuli. *Journal of Neurophysiology*, **32**, 1025–1043.

CAMPBELL, J. N. and TAUB, A. (1973) Local analgesia from percutaneous electrical stimulation. *Archives of Neurology, Chicago*, **28**, 347–350.

CERVERO, F., IGGO, A and OGAWA, H. (1976) Nociceptor driven dorsal horn neurones in the lumbar spinal cord of the cat. *Pain*, **2**, 5–24.

CHRISTENSEN, B. N and PERL, E. R. (1970) Spinal neurons specifically excited by noxious or thermal stimuli. *Journal of Neurophysiology*, **33**, 293–307.

COLLINS, W. F. Jr, NULSEN, F. E. and RANDT, C. T. (1960) Relation of peripheral nerve size and sensation in man. *Archives of Neurology, Chicago*, **3**, 381–385.

—— and RANDT, C. T (1960) Midbrain evoked responses relating to peripheral unmyelinated C fibres in cat. *Journal of Neurophysiology*, **23**, 47–53.

DENNY-BROWN, D., KIRK, E. J. and YANAGISAWA, N. (1973) The tract of Lissauer in relation to sensory transmission in the dorsal horn of spinal cord in the macaque. *Journal of Comparative Neurology*, **151**, 175-200.

DEVOR, M. and WALL, P. D. (1978) The physiology of sensation after peripheral nerve injury, regeneration and neuroma formation. In: *The Physiology and Pathobiology of Axons*. Edited by S. G. Waxman. New York: Raven Press.

DIAMOND, J. (1959) The effects of injecting acetylcholine into normal and regenerating nerves. *Journal of Physiology*, **145**, 611-629.

DILLY, P. N., WALL, P. D. and WEBSTER, L. E. (1968) Cells of origin of the spinothalamic tract in the cat and rat. *Experimental Neurology*, **21**, 550-562.

DOUGLAS, W. W. and RITCHIE, J. M. (1957) Non-medullated fibres in the saphenous nerve which signal touch. *Journal of Physiology*, **139**, 385-399.

DYCK, P. J., LAMBERT, E. H. and NICHOLS, P. (1971) Sensation related to compound action potentials and number and sizes of myelinated and unmyelinated fibres of sural nerve in health Friedrich's ataxia, hereditary sensory neuropathy, and tabes dorsalis. In: *Handbook of EEG and Clinical Neurophysiology*. Edited by A. Bemond. Amsterdam: Elsevier, vol. 9, pp. 83-118.

—— —— and O'BRIEN, P. C. (1976) Pain in peripheral neuropathy related to rate and kind of fibre degeneration. *Neurology, Minneapolis*, **22**, 466-471.

—— THOMAS, P. K. and LAMBERT, E. H., Editors (1974) *Peripheral Neuropathy*, Philadelphia: Saunders.

ECCLES, J. C. (1964) Presynaptic inhibition in the spinal cord. In: *Progress in Brain Research. Vol. 12, Physiology of Spinal Neurons*. Edited by J. C. Eccles and J. P. Schadé, Amsterdam: Elsevier.

ENGBERG, I., LUNDBERG, A. and RYALL, R. W. (1968) Is the tonic decerebrate inhibition of reflex paths mediated by monoaminergic pathways. *Acta Physiologica Scandanavica*, **72**, 123-133.

ERULKAR, S. D., SPRAGUE, J. M., WHITSEL, B. L., DOGAN, S. and JANETTA, P. J. (1966) Organisation of the vestibular projection to the spinal cord of cat. *Journal of Neurophysiology*, **29**, 626-664.

FETZ, E. (1968) Pyramidal tract effects on interneurons in cat spinal cord. *Journal of Neurophysiology*, **31**, 69-80.

FIELDS, H. L., BASBAUM, A. I., CLANTON, C. H. and ANDERSON, S. D. (1977) Nucleus raphe magnus inhibition of spinal cord dorsal horn neurons. *Proceedings of the National Academy of Sciences*. In press.

FOREMAN, R. D., BEALL, J. E., APPLEBAUM, A. E., COULTER, J. D. and WILLIS, W. D. (1976) Effects of dorsal column stimulation on primate spinothalamic tract neurons. *Journal of Neurophysiology*, **39**, 534-546.

HEIMER, L. and WALL, P. D. (1968) The dorsal root distribution of the substantia gelatinosa of the rat with a note on the distribution in the cat. *Experimental Brain Research*, **6**, 89-99.

HIGGINS, J. D., TURSKY, B. and SCHWARTZ, G. E. (1971) Shock elicited pain and its reduction by concurrent tactile stimulation. *Science*, **72**, 866-867.

HILLMAN, P. and WALL, P. D. (1969) Inhibitory and excitatory factors controlling lamina 5 cells. *Experimental Brain Research*, **9**, 284-306.

HONGO, T., JANKOWSKA, E. and LUNDBERG, A. (1968) Post-synaptic excitation and inhibition from primary afferents in neurons of the spinocervical tract. *Journal of Physiology*, **199**, 569-592.

HOWLAND, B., WALL, P. D., LETTVIN, J. Y., MCCULLOCH, W. C. and PITTS, W. (1955) Reflex inhibition by dorsal root interaction. *Journal of Neurophysiology*, **18**, 1–17.

HUNT, C. C. and MCINTYRE, A. K. (1960) An analysis of fibre diameter and receptor characteristics of myelinated cutaneous afferents in cat. *Journal of Physiology*, **153**, 99–112.

IGGO, A. (1960) Cutaneous mechanoreceptors with afferent C fibres. *Journal of Physiology*, **152**, 337–353.

—— (1973) *Somatosensory System*, Berlin: Springer-Verlag, pp. 29–78.

IGNELZI, R. J and NYQUIST, J. K (1976) Direct effect of electrical stimulation on peripheral nerve evoked activity. *Journal of Neurosurgery*, **45**, 159–165.

KERR, F. W. L. (1975) Neuroanatomical substrates of nociception in the spinal cord. *Pain*, **1**, 325–356.

KOCEN, R. S. and THOMAS, P. K. (1970) Peripheral nerve involvement in Fabry's disease. *Archives of Neurology, Chicago*, **22**, 81–89.

KUMAZAWA, T. and PERL, E. R. (1978) Primate cutaneous receptors with unmyelinated fibres and their projections to the substantia gelatinosa. *Journal de Physiologie, Paris.* In press.

—— —— BURGESS, P. R. and WHITEHORN, D. (1975) Ascending projections from marginal zone neurons. *Journal of Comparative Neurology*, **162**, 1–12.

LINDBLOM, U. and MEYERSON, B. A. (1975) Influence on touch, vibration and cutaneous pain of dorsal column stimulation in man. *Pain*, **1**, 257–270.

LONG, D. M. and HAGFORS, N. (1975) Electrical stimulation in the nervous system: the current status of electrical stimulation of the nervous system for the relief of pain. *Pain*, **1**, 109–124.

MAYER, D. J. and LIEBESKIND, J. C. (1974) Pain reduction by focal electrical stimulation of the brain. *Brain Research, Amsterdam*, **68**, 73–93.

—— and PRICE, D. D. (1976) Central nervous system mechanisms of analgesia. *Pain*, **2**, 379–404.

—— —— and BECKER, D. P. (1975) Neurophysiological characterisation of the anterolateral spinal cord neurons contributing to pain perception in man. *Pain*, **1**, 51–58.

MELZACK, R. (1973) *The Puzzle of Pain.* Harmondsworth, England: Penguin Education.

—— and WALL, P. D. (1962) On the nature of cutaneous sensory mechanisms. *Brain*, **85**, 331–356.

—— —— (1965) Pain mechanisms: a new theory. *Science*, **150**, 971–979.

MENDELL, L. M. (1966) Physiological properties of unmyelinated fibre projection to the spinal cord. *Experimental Neurology*, **16**, 316–332.

NATHAN, P. W. (1976) The gate-control theory of pain. A critical review. *Brain*, **99**, 123–158.

—— and WALL, P. D. (1974) Treatment of post-herpetic neuralgia by prolonged electric stimulation. *British Medical Journal*, **3**, 645–647.

NOORDENBOS, W. (1959) *Pain.* Amsterdam: Elsevier.

OLIVERAS, J. L., REDJEMI, J. M., GUILBAUD, G. and LIEBESKIND, J. C. (1974) Behavioural and electrophysiological evidence of pain inhibition from midbrain stimulation in the cat. *Experimental Brain Research*, **20**, 32–44.

POMERANZ, B., WALL, P. D. and WEBER, W. V. (1968) Cord cells responding to fine myelinated afferents from viscera, muscle and skin. *Journal of Physiology*, **199**, 511–532.

PRICE, D. D. and MAYER, D. J. (1975) Neurophysiological characterisation of the anterolateral quadrant neurons subserving pain in *macaca mulatta. Pain*, **1**, 59–72.

REYNOLDS, D. V. (1969) Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science*, **164**, 444–445.

SATRON, R. and GOLDSTEIN, M. N. (1973) Pain perception: modification of threshold of intolerance and cortical potentials by cutaneous stimulation. *Science*, **180**, 1201–1202.

SCHOENE, W. C., ASBURY, A. L., ASTROM, K. E. and MASTERS, R. (1970) Hereditary sensory neuropathy. *Journal of Neurological Sciences*, **11**, 463–472.

SHERRINGTON, C. S. (1903) Qualitative difference of spinal reflex corresponding to qualitative difference of cutaneous stimulus. *Journal of Physiology*, **30**, 39–46.

—— and SOWTON, S. C. M. (1915) Observations of reflex responses to single break shocks. *Journal of Physiology*, **49**, 331–345.

STERNBACH, R A. and TURSKY, B. (1964) On the psychophysical power function in electric shock *Psychonomic Science*, **1**, 217–243.

SZENTAGOTHAI, J. (1964) Propriospinal pathways and their synapses. In: *Progress in Brain Research. 2, Organisation of Spinal Cord.* Edited by J. C. Eccles and J. P. Schadé. Amsterdam: Elsevier.

THOMAS, P. K. (1975) The anatomical substratum of pain. *Canadian Journal of Neurological Science*, **1**, 92–97.

TOREBJORK, H. E. and HALLIN, R. G. (1973) Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human nerves. *Experimental Brain Research*, **16**, 321–332.

—— —— (1974) Identification of afferent C units in intact human skin nerves. *Brain Research, Amsterdam*, **67**, 387–403.

TREVINO, D., COULTER, J. D. and WILLIS, W. D. (1973) Location of cells of origin of the spinothalamic tract in the lumbar enlargement of the monkey. *Journal of Neurophysiology*, **36**, 750–761.

VAN HEES, J. and GYBELS, J. M. (1972) Pain related to single afferent C fibres in human skin. *Brain Research, Amsterdam*, **48**, 397–400.

WALL, P. D. (1959) Repetitive discharge of neurons. *Journal of Neurophysiology*, **22**, 305–320.

—— (1962) The origin of a spinal cord slow potential. *Journal of Physiology*, **164**, 508–526.

—— (1967) The laminar organization of dorsal horn and effects of descending impulses. *Journal of Physiology*, **188**, 403–423.

—— (1968) Organization of cord cells which transmit sensory information. In: *The Skin Senses.* Edited by D. R. Kenshalo. Springfield: Thomas, pp. 512–533.

—— (1973) Dorsal horn electrophysiology. In: *Handbook of Sensory Physiology*, Vol. 2. Berlin: Springer-Verlag, pp. 253–270.

—— (1974) The future of attacks on pain. In: *Advances in Neurology. Vol. 4. Pain.* Edited by J. J. Bonica. New York: Raven Press.

—— (1976) Modulation of pain by non-painful events. In: *Advances in Pain Research and Therapy.* Vol. 1 Edited by J. J. Bonica. New York: Raven Press.

WALL, P. D. and GUTNICK, M. (1974*a*) Ongoing activity in peripheral nerves: II. The physiology and pharmacology of impulses originating in a neuroma. *Experimental Neurology*, **43,** 580–593.

—— —— (1974*b*) Properties of afferent nerve impulses originating from a neuroma. *Nature, London*, **248,** 740–743.

—— and SWEET, W. H. (1967) Temporary abolition of pain in man. *Science*, **155,** 108–109.

WHITE, J. C. and SWEET, W. H. (1969) *Pain and the Neurosurgeon*. Springfield: Thomas.

ZOTTERMAN, Y. (1939) Touch, pain and tickling. *Journal of Physiology*, **95,** 1–28.

(*Received March 8, 1977*)

Brain (1978), **101**, 19–34.

SOME FREQUENCY RESPONSE CHARACTERISTICS OF PARKINSONISM ON PURSUIT TRACKING

by KENNETH FLOWERS[1]

(*From the MRC Brain and Perception Laboratory, University of Bristol Medical School, Bristol BS8 1TD*)

INTRODUCTION

THERE has been considerable interest in recent years in the impairment of voluntary movement shown by patients suffering from Parkinson's disease. Most of the work reported previously has been concerned with discrete movements, emphasizing the difficulties these patients have in programming movement sequences (Perret, Eggenberger and Siegfried, 1970), in carrying out two actions simultaneously (Schwab, Chafetz and Walker, 1954; Horne, 1973) or in correcting erroneous movements (Angel, Alston and Higgins, 1970). Individual aiming movements also appear to be abnormal in these patients (Flowers, 1975, 1976), leading the present author to suggest that the parkinsonian deficit may be described as a loss of skill, especially of the 'programs' of movement learnt in the course of normal perceptual motor development. (These programs allow quick and efficient movement on the basis of a predictive selection of actions which are known to be more or less appropriate to the particular conditions of the task in hand). If so, these patients should also have difficulty in controlling continuous movement, where the subject has to initiate not just individual discrete actions, but a smooth continuously-graded control of the force being applied and of its timing. A good way to measure this is in terms of frequency response, a technique borrowed from engineering and the specification of physical systems, and applied previously to normal human pursuit tracking performance (e.g. Noble, Fitts and Warren, 1955).

Stark (1968), Cassell, Shaw and Stern (1973) and Eidelberg and Dunmire (1973) tested parkinsonian subjects on a continuous tracking task, finding them less efficient than controls in terms of tracking lag and relative amplitude of response (amplitude proportional to that of the input). Their tracks, however, were irregular and largely unpredictable, so that the tracking movements had to be initiated mainly as serial responses to the position of the target from moment to moment, rather than generated spontaneously from their knowledge of the shape and characteristics of the track. With a regular sinusoidal target motion, however, normal subjects usually perform better than on irregular tracks by switching to a predictive mode of control based on some 'model' of the target motion, which allows them to reduce their tracking lag and produce a smooth continuous movement. Noble *et al.* suggested that the normal tracker works in this way: 'In a task that requires him to make his response output correspond in time and space to a continuously and rapidly changing stimulus, S does not respond directly to the stimulus at all—instead, he puts out a continuous predicted response, observes the relation between his output and the stimulus pattern, and at periodic intervals makes necessary changes in his predictions.' In other words, he changes from control through external information, to control through internal information or an 'internal model' of the movement to be generated (Kelley, 1968; Gregory, 1970).

---

[1] Present address: Department of Psychology, The University, Hull HU6 7RX.

Frequency response functions indicate the amplitude and phase relationships between input and output for sinusoidal input signals of different frequencies, where the temporal relation between input and output is critical (especially at higher frequencies). Studies on well-practised normal operators (reviewed by Poulton, 1974) have shown that tracking becomes worse as the task frequency increases, although the size of the error begins to rise sharply only at frequencies of 1·5 Hz and above. Unlike most physical systems, where the amplitude decreases after some critical frequency is reached, humans tend to maintain the amplitude of their response, but lose synchronization with the input. When this occurs, they require some constant 'sampling period' to observe the target and their own output before attempting to correct the discrepancy; alternatively they may continue to generate an output at a different amplitude or frequency to that of the input, that is, one which is more or less independent of the target motion. Other sources of error include variability in output amplitude, and consistent over- or undershooting of the target. All these appear more pronounced as the frequency of the input increases, but improve with practice as skill develops.

In this study the performance of a group of parkinsonian subjects was compared with that of a control group of relatively unsophisticated and unpractised normals, to see whether the patients' tracking was abnormal, and if so, in what way. Do they get relatively worse as frequency increases (as suggested in a brief report by Eidelberg and Dunmire, 1973)? Do they break down at a lower frequency of input, and if so, what kind of strategy do they then adopt? Three frequencies of sinewave were used, 0·17 Hz (slow), 0·50 Hz (fast) and 1·00 Hz (very fast), the last of these being presented at smaller amplitudes (80 and 40 mm) as well as the standard one of 125 mm. In addition, two sweep tracks were presented, where the frequency increased throughout the trials. These tested the ability of subjects to change the speed of their movements in a steady and controlled fashion.

As well as these sinusoidal tracks, three other tracks were presented for comparison; a slow ramp track of 0·11 Hz which required a constant velocity rather than a sinusoidal movement; and two irregular 'noise' tracks, whose mean frequencies were about the same as those of the 'slow' and 'fast' sine-waves. These latter gave an estimate of the subject's ability to track in a 'response' mode rather than in a 'predictive' one; normal subjects showed a substantial advantage in tracking regular sinusoidal movements compared to these unpredictable ones, as explained above.

METHOD

Subjects

The Parkinsonian Group comprised 15 subjects, 8 men and 7 women, all outpatients with two or more years' history of the disease. Their ages ranged from 38 to 74 years with a mean of 60·1. All but 2 were being treated with L-Dopa or Sinemet, which they claimed had greatly improved their condition (mainly as regards the tremor and rigidity features of their illness). Some patients had undergone surgery for the disease, which they also claimed had ameliorated their symptoms. In no case were the classical symptoms of tremor, rigidity and bradykinesia present to more than a moderate degree. Table 1 gives the clinical assessment of all the patients at the time of testing.

The Control Group comprised 16 paid volunteers, 15 of them drawn from the non-academic staff of the University or their relatives, and one academic volunteer. There were 9 men and 7 women, ages ranging from 38 to 71 years with a mean of 56·7. Their experience of the apparatus and testing was matched with that of the patients (if anything, they had less practice both within sessions and in the number of sessions) and they were tested with similar procedures to the patients. None of them had a history of nervous disease or serious head injury, and none were taking drugs which would directly affect the central nervous system.

One patient in the Parkinsonian Group was mixed-handed with a general preference for the left hand All the other subjects were fully right-handed; the preferred hand was used in all cases regardless of which one appeared to be worst affected by the illness, as all subjects reported this felt most comfortable for them.

Apparatus

A large screen oscilloscope (Lanscope Model 419A Display Scope with a 17-inch short persistence TV-type tube) was used for the display. Beam-switching provided two independently moved markers. The target marker was a small (3 mm diameter) circle generated as a Lissajous from an oscillator with 90 degrees phase shift. The tracked waveform was produced by means of an Advance VLF generator (type SG88) capable of providing any repetitive function, including repeatable noise. The subject's control marker was a small dot precisely following the movement of the joystick. The subject's task was to make the control spot match the movement of the target as closely as he could, as it moved to left and right in one dimension across the centre of the screen in various wave-forms, keeping it in the centre of the circle if possible. The joystick gain was set so that the movement of the spot was virtually equal to that of the hand in the horizontal plane. The joystick was mounted in precision gimbal bearings (modified from a gyroscope) which allowed movement laterally (left–right) and antero-posteriorly (forward and back) with very low friction and inertia. It was fitted with a pair of linear potentiometers, such that movement of the joystick knob produced an equal horizontal movement of the spot on the screen (movement forward and back was not registered on the screen, nor recorded).

Tracking was recorded on a UV recorder (SE Laboratories (EMI) type 3006/DL) for visual inspection, and by means of punched tape for numerical analysis. An eight-channel multiplexer sampled the outputs from the oscilloscope and joystick at intervals of 80 ms and fed through an A-D converter to a tape-punch.

P25684

UNIVERSITY COLLE
LIB

TABLE 1. CLINICAL ASSESSMENT OF DISABILITY IN THE PARKINSONIAN GROUP

Subject	*Sex*	*Age*	*Approx. time since onset (yrs)*	*Tremor*	*Rigidity*	*Bradykinesia and associated abnormalities*	*Social disability*	*Drugs, etc.*
1. D.S.	M	52	12	Slight at rest.	Very slight.	Does not swing arms Otherwise not marked.	Independent. Not working because of speech difficulty (teacher). Writing small, spidery.	L. thalamotomy 1964 for R. arm. L-Dopa 500 mg b.d. Benzhexol 5 mg b.d.
2. A.S.	M	63	5	Slight at rest.	Very slight.	Slight, but handwriting gets smaller.	Independent. Retired civil servant. Mild disability, e.g. cutting meat.	L-Dopa 3 g daily. Methixene HCL 5 mg q.d.s.
3. N.B.	M	63	4	Very slight in R. arm at rest.	Slight in both arms.	Slight.	Independent. Retired insurance executive. Complains of blurred vision, but ophthalmology normal.	Sinemet 2½ tabs daily. Valium 2½ mg t.d.s.
4. F.H.	M	59	2	Slight in R. arm, hand at rest.	Mild in R arm.	Moderate. R. foot drags in walking.	Independent. Works as stonemason.	Sinemet 2 tabs daily.
5. F.W.	M	68	3	Moderate in R. arm at rest.	Mild cogwheel in R. arm.	Mild to moderate R. foot drags slightly in walking. Difficulty in rising from armchair.	Independent. Retired woodcarver. R. hand lost power and control. Handwriting a scribble.	Sinemet 1 tab b.d. Artane 2 mg b.d.
6. P.T.	M	56	2	Very slight in L. leg.	None noticeable.	Mild in both arms, L > R.	Independent. Still working (vicar) Difficulty in fingerwork playing french horn. ? intellectual deterioration.	Sinemet ½ tab q.d.s.
7 M.W	F	39	6	None noticeable.	Slight in L. arm, leg	Mild to moderate in L. arm, leg.	Independent. Working as clerk. Intermittently stiff and awkward in L. arm, leg.	L-Dopa 2½ mg × 6 daily.
8. V.W.	F	74	11	Moderate at rest.	Moderate.	Mild to moderate.	Independent. Housewife.	R. thalamotomy 1967. L-Dopa 1 g t.d.s.
9. I.S.	F	74	12	Moderate in both arms at rest (R > L).	Mild cogwheel in both arms.	Slight Difficulty in walking up stairs, or rising from low chair.	Independent. Housewife. Difficulty peeling potatoes. Writing scribbly.	Artane 2 mg q.d.s.
10 E.W.	F	75	2	Occasionally, slight in L. arm at rest.	Mild in L. arm	Mild in both arms, L > R. Occasionally drags L. leg when walking.	Independent Housewife	Sinemet ½ tab t.d.s.

11. M.R.	F	55	12	None noticeable.	Mild in both arms	Mild in both arms, hands. Walks quickly.	Independent. Housewife.	L-Dopa 2 g daily
12. M.P.	F	47	2	Intermittent slight to moderate at rest.	Slight.	Moderate.	Independent. Housewife. Difficulty in dressing. Unable to sew. Writing bad.	L-Dopa 3½ g daily. Amantadine 100 mg b d. Debendox (Merrell): mixture of Dicyclomine HCL and dixylamine succinate and pyridoxine HCL 10 mg each (anti-nausea).
13. M.M.	F	50	4	Very slight at rest. Rhythmic 7–8 cps.	None noticeable.	Does not swing R. arm.	Independent. Housewife. Can write and knit	No drugs.
14. G.D.	M	67	9	Moderate in both hands, intermittent.	Mild cogwheel in all limbs.	Moderate, generalized.	Severe Needs help to dress. Falls. Poor memory. Retired.	Sinemet ½ tab t.d.s. Disipal 50 mg t.d.s. Artane 5 mg t.d.s.
15. A J.	M	62	8	Moderate to severe, variable at rest.	Slight.	Mild bradykinesia. Paucity of spontaneous movement.	Independent. Confused at night. Retired.	L-Dopa 750 mg t.d.s. Orphenadrine HCL 200 mg daily.

Target Tracks

Details of the various wave-forms used in the study are given in Table 2. The 'noise' tracks were produced by blanking off all but two portions of the VLF noise disc so that the same parts of the disc were used for all subjects. Repeated trials used the two portions alternately to reduce any possible (though unlikely) learning of the tracks themselves. In the sine-wave-sweep conditions, the frequency was set at the lower value at the beginning of the trial, and increased automatically throughout the run until it reached the higher value. Subjects had therefore to adjust the speed of their movement continuously during the run. Control subjects were given the 80 and 40 mm sine-wave conditions at the higher 1·5 Hz frequency; the patients were given these conditions at the lower 1·0 Hz frequency.

TABLE 2. WAVE-FORM CHARACTERISTICS OF TRACKS USED IN THE STUDY

Condition	*Amplitude on screen (mm)*	*Frequency*	*Length of test run*	
			Cycles	*Time(s)*
Slow sine	125	0·17 Hz	8	48
Slow sine sweep	125	0·17–0·50 Hz	18	60
Fast sine	125	0·50 Hz	16	32
Fast sine sweep	125	0·50–1·00 Hz	25	35
V. fast sine	125	1·00 Hz	32	32
VV. fast sine 8	80	1·50 or 1·00 Hz	24 or 16	16
VV. fast sine 4	40	1·50 or 1·00 Hz	24 or 16	16
Slow noise	Approx. 110 mm average	Approx. 0·17 Hz average	Approx. 6	50
Fast noise	Approx. 110 mm average	Approx. 0·50 Hz average	Approx. 16	35
Ramp	125	0·11 Hz	6	54

Procedure

Subjects sat squarely in front of a table with the display set at head height 560 mm away from its outer edge. The joystick was mounted so that it projected through a square hole 200 mm × 200 mm in size cut in the table top, and the subject positioned so that he could grasp the top of the lever securely with his arm resting on the table at the elbow.

Each control subject contributed test runs for each condition on at least two separate occasions. They always tracked the ramp before the 125 mm sine-waves, and this 'block' was either preceded or followed on alternate sessions by the noise tracks. Low frequencies always preceded high frequencies in all wave-forms. The sweep and 80 mm or 40 mm sine-wave tracks were always presented after the 125 mm sine-wave conditions. Usually one or two runs were made in each condition on each session. Total testing time was about an hour, with subjects allowed up to 60 s of practice at each condition before tackling the test run, a rest for 45–60 s between runs, and a rest of 4–5 min between each wave-form.

Three patients contributed test runs on one occasion only, and did not perform on the sweep or smaller-amplitude sine conditions; the other 12 were tested on at least three sessions, and contributed at least four runs to their scores at each condition. For practical reasons the length and order of testing varied for different subjects on different days, but with the following constraints: subjects always performed on the noise tracks when they performed on the 125 mm regular tracks, and they always went through the fast sine-waves whenever performing the 80 mm and 40 mm conditions or the sweep conditions. Only 9 subjects were tested on the 80 mm or 40 mm sine-waves. All subjects had performed previously on experiments with step wave-forms, and were therefore familiar with the control-spot dynamics. They were allowed to practise each condition before undertaking the test runs, and were allowed as much rest as they required between trials, with at least five minutes between wave-forms. Testing was stopped whenever the patient expressed tiredness or reluctance to continue. Test runs were stopped and discarded at any time when the patient's performance broke down during the period of the test run while the punch tape was running, except in the case of the fast-sine-sweep, where subjects were instructed to continue until told to stop by the experimenter (even if they did stop or lose synchrony for a time) so that their performance could be inspected on the UV record.

No instructions or suggestions were given to the subjects as to the strategy they should adopt, other than telling them to try to keep the spot in line with the circle as closely as they could.

Analysis of Results

The punch-tape data was processed by computer with a cross-correlation program which calculated the root-mean-squared error for different time-displacements of the operator position compared to that of the target. This yielded three scores: (i) root-mean-squared error at delay zero, that is, normal RMS error score; (ii) average tracking lag or lead which gives the least mean-squared-error score, indicating the average tracking lag or lead of the subject; (iii) best error score, that is, error at the average lag/lead. Lag/lead was calculated to the nearest 80 ms ahead of or behind the target up to a maximum of ±480 ms.

The median value of the scores obtained from each subject in the various test runs he performed was taken as the representative score for that subject. The median seemed a fairer estimate of performance than the mean, since it is less affected by large errors on single runs; the rather more erratic parkinsonian performance is thus favoured in comparison with normal scores. Examination of the data for each subject showed that there were no consistent trends towards improvement or deterioration with successive trials; some patients improved on later sessions, others got worse, but most varied both ways in the course of their experience of tracking. Nor was there any reliable tendency for second or third runs within a session to improve (practice, learning) or deteriorate (fatigue, loss of concentration, etc.).

Group mean and standard deviation scores were then calculated to give over-all group values. Two-tailed t-tests were used for comparison within subjects, and two-tailed variance ratios and Mann-Whitney U-tests used for comparisons between groups.

RESULTS

Frequency Response

Fig. 1 shows root-mean-squared (RMS) error scores for the two experimental groups on the ten conditions tested. The Parkinsonian error scores are worse than the control scores on all five sine-wave tracks, and on the ramp track too (differences are significant at level of $P < 0{\cdot}05$ or better, although variances are greater in the Parkinsonian Group also in all but the 1·0 Hz and fast-sweep conditions, with F ratios significant at level $P < 0{\cdot}05$ or better). On the fastest sine track (1·0 Hz) the Parkinsonian scores approach the level of error obtained when the subject holds the stick stationary and does not track at all. This 'do-nothing' error level is shown by the horizontal bar. It thus appears that these patients are worse than normals at generating regular sinusoidal movements to match a given target movement; their deficit is found across a range of frequencies and does not increase markedly as the frequency tracked increases, but by 1·0 Hz many of them are doing no better than they would do by holding the stick still and doing nothing.

Error scores for the slower noise condition show no reliable difference between the groups, while those for the faster noise track approach the 'do-nothing' level for both groups. Perusal of the individual median scores of the patients shows that only 6 of the 15 subjects' error scores fall more than one standard deviation above the Control Group average on the two noise tracks, while 11 and 10 respectively do so on the equivalent sine tracks (0·17 and 0·5 Hz). The difference between the

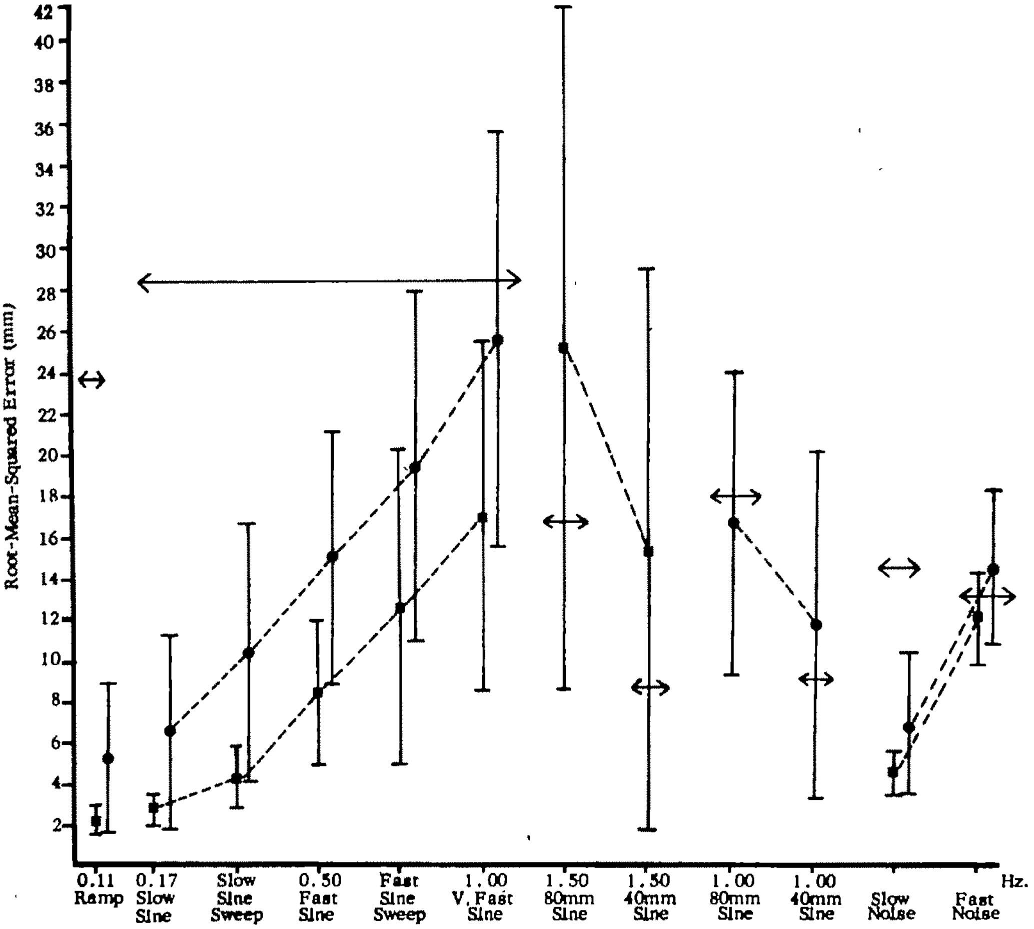


FIG. 1. RMS error scores. The graph shows mean and standard deviation scores for each group on the ten conditions of pursuit tracking tested. ■ = Controls ● = Parkinsonian patients. The horizontal arrowed lines indicate the 'do-nothing' error level obtained when the joystick is held stationary throughout the trial.

groups, therefore, is more pronounced for the regular sinusoidal and ramp tracks than it is for the irregular ones. Furthermore, the Parkinsonian subjects show no reliable improvement in error score when the slow or fast noise tracks are compared with the sine track of equivalent frequency, while a similar comparison for the Control Group shows a highly significant difference (sine error better than noise error at level of $P < 0{\cdot}001$ in both cases). This suggests that the Parkinsonian patient may be tracking the regular wave-forms at the same level as if they were irregular, that is, no better than if they were following them from moment to moment rather than generating the required shape of track spontaneously.

Normal subjects tracking the 80 mm and 40 mm amplitude sine-waves at 1·5 Hz have error scores well above the 'do-nothing' level. This appears to be the maximum frequency these relatively unsophisticated and unpractised subjects can track at all successfully, whatever the amplitude. Reducing the amplitude at 1·0 Hz does not help the Parkinsonian Group either, so their deficit is also to a large extent independent of amplitude, and the 'do-nothing' level is reached at a lower frequency.

Phase Lags

The average tracking lag/lead found in the two groups by the cross-correlation procedure is shown in fig. 2 for the ten conditions. The Control Group tend to keep about 25–50 ms behind the target in all the regular conditions, and are substantially further behind when tracking noise, as one would expect. The lag on the faster noise track is on average some 35 ms less than the RT shown by these subjects on an acquisition task (Flowers, 1976). The Parkinsonian Group's average lag is greater in all conditions (differences cf. controls significant at level of $P < 0{\cdot}05$ or better in all cases) indicating a less accurate matching, or timing, of the movement. Both groups, however, show a highly significant improvement in their lag on the regular tracks than on the noise tracks, so the patients are also able to use the regular nature of the sine and ramp wave-forms to reduce their RT lag to some extent. The smaller difference found on the faster frequencies may be an underestimate based on the fact that only trials where the subject matched the movement of the target for the 30–35 s period were used in the calculation; subjects who get more than 300 ms or so behind on this condition tend to break down and stop completely, and the trial is therefore discarded. This occurred more often in the Parkinsonian Group than in the Control Group, 6 patients breaking down on a total of thirteen occasions compared to 4 normals stopping on five occasions.

The error scores obtained after cross-correlation (the 'best error' scores) were compared in the same way as the initial RMS scores. All the relationships and differences were preserved after the cross-correlation procedure. Parkinsonian error scores were worse than control scores on all the regular tracks, and at 1·0 Hz they still approached the 'do-nothing' level, although reduced by a certain amount. There was some suggestion that the difference between patient and normal scores widened with increasing frequency, but this was not marked. The Parkinsonian deficit in RMS error score on the regular tracks, therefore, is not explained solely in terms of increased tracking lag, since they still show a considerably increased error, compared to the controls, after this has been allowed for.

Loss of Synchrony in Sine-wave Sweep

As the frequency of target movement increases in the sweep condition, subjects lose the ability to keep up with it at the full amplitude and are forced to choose

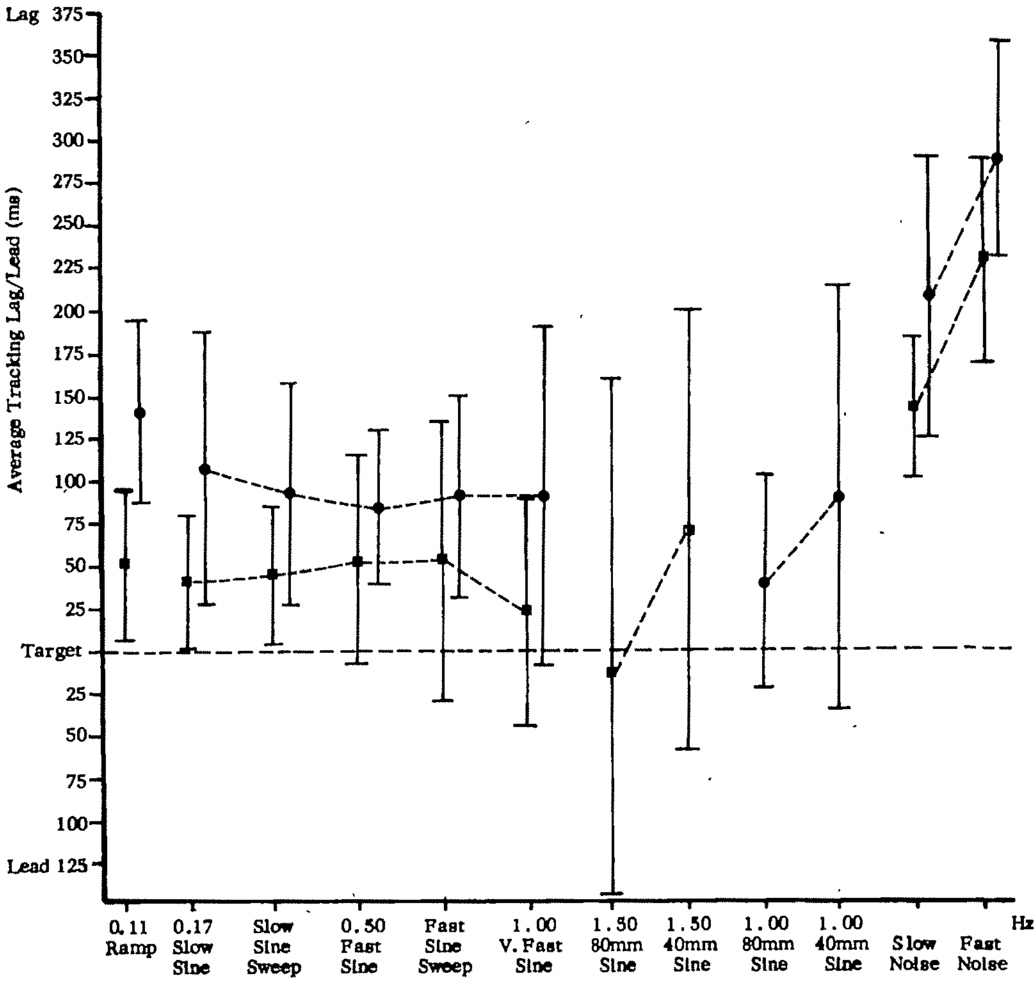


FIG. 2. Average tracking lag or lead. The graph shows mean and standard deviation scores for each group on the ten conditions of pursuit tracking tested. ■ = Controls. ● = Parkinsonian patients.

between reducing the amplitude of their tracking action or losing synchrony with the target. At some point even those who reduce the amplitude of movement lose synchrony. Each subject in this study performed on four trials with the slow sweep (frequency increasing from 0·17–0·5 Hz in 60 s) and four trials with the fast sweep (frequency increasing from 0·5–1·0 Hz in 35 s and then from 1·00 to 4·00 Hz or more in another 35 s). The UV records were examined to see at what frequency the subject's response lost touch with the target, how it broke down, and what the subject did after losing synchrony. The 'break-down point' was taken as either (i) the point at which the subject became one cycle or more behind the target, without re-synchronizing again at an amplitude of at least two-thirds the target amplitude (sometimes subjects lost a single cycle but picked up the target again and continued tracking adequately for several seconds longer); or (ii) the point at which the subject's response was reduced in amplitude to less than two-thirds of the target amplitude (again providing the response did not regain a reasonable amplitude later). As some subjects, especially in the Control Group, progressively reduced the amplitude of response to keep in time, the point at which they lost synchrony altogether was also noted.

On the slow sweep, all the Controls and all but one of the Parkinsonian patients managed to keep up with the target movement fairly closely throughout the trial. On the fast sweep, Control subjects broke down in one or other feature of their response at about 1·42 Hz (median 1·32 Hz, mean 1·48 Hz, SD 0·59 Hz). The majority of them (9 subjects) reduced the amplitude of their response to keep in time with the target; 3 subjects sometimes reduced amplitude to keep in time and on other occasions kept amplitude but lost synchrony; and 4 subjects lost both at the break-down point, failing to match either characteristic of the target motion. The Parkinsonian patients lost touch with the target earlier on average (median frequency of break-down 0·97 Hz, mean 1·05 Hz, SD 0·37 Hz). Three patients reduced amplitude but kept synchrony, 2 kept their amplitude but lost synchrony and the other 7 lost both, tending to stop completely, or go into small steady oscillations at about the frequency of their break-down point, or make erratic movements unrelated to the target motion at all. The difference between break-down points in the two groups is significantly statistically (Mann-Whitney U = 47, $P < 0{\cdot}05$). The data suggests that subjects in both groups break down on the sweep condition at about the same frequency at which their error approaches the 'do-nothing' level in the other sine-wave conditions (1·0 Hz and 1·5 Hz respectively for patients and controls). One difference between them is that controls tend to keep in time with the target motion ('getting the rhythm' is how many of them described it) though forced to reduce amplitude, while most of the patients lost synchrony as well as amplitude at the break-down point, thus losing the pattern of movement completely. This is confirmed when the frequency at which the response is lost altogether is calculated. The 3 patients who kept time beyond the break-down point only did so for 0·09, 0·22 and 0·59 Hz respectively, and the group frequency as a whole is hardly changed (median frequency of break-down is now

1·01 Hz, the mean 1·12 Hz and the SD 0·45 Hz). The 9 control subjects who keep in time beyond the break-down point, however, stay with the target for up to another 0·47 Hz on average, and the group frequency is substantially improved (median frequency of break-down 1·62 Hz, mean 1·73 Hz, SD 0·61 Hz).

DISCUSSION

Although sinusoidal movements are the easiest and most 'natural' movements a subject can be asked to make, Parkinsonian subjects appear to be abnormal in the way they generate them. Whether the motion is slow, with only gradual changes in rate or direction, or fast and rapidly-changing, error scores indicate that the Parkinsonian's accuracy of matching the target movement is considerably worse than normal. The difference is only partly one of increased tracking lag, since when this is accounted for, the error scores of the patients are still significantly greater than those of the Controls. It is also not just a feature of large amplitude movements, since there is little improvement on the smaller amplitude conditions of 80 and 40 mm. It seems, therefore, that parkinsonism affects the ability to produce smooth continuous action as well as individual movements.

Surprisingly, perhaps, the difference is greater for the regular tracks than it is for the more usual pseudo-random unpredictable 'noise' tracks, although the patients are notably slower on the latter. This may be because the particular advantages of predictive control from an 'internal model' are not as apparent for the irregular condition, and so the Controls cannot improve their performance on this basis compared with the patients.

Learning does not seem to play much part in the patients' performance, since as many of this group obtained worse scores in later trials as obtained better ones. Testing sessions were usually a week or so, and sometimes several months apart, so it is unlikely that any great learning effect took place in any of the subjects tested here. (Other effects, such as transfer, fatigue or deterioration in the subject's condition may have interacted with practice effects to obscure them, but there were no signs of consistent changes due to these either.) Whether prolonged practice would allow the patients to improve to any great extent is impossible to say, but certainly the patients lack the normal ability to match a given target movement in terms of its amplitude and frequency within a minute or two of tracking it. Previous work (Flowers, 1976) which found no improvement in individual aiming movements with practice, suggests that even prolonged practice may not be of benefit to these patients.

With an amplitude of 125 mm across the screen viewed at a distance of 560 mm, the target moved through a visual angle of 12° 44′ and thus almost certainly required movement of the eyes to follow it. One possibility is that the Parkinsonian patients were deficient in their visual tracking of the target, which would make it difficult for them to control their manual tracking. The possibility was checked in 4 subjects with electro-oculography, and no deficits in the patients' eye-tracking was found. (This will be reported separately later.) The manual tracking abnormality in these patients, therefore, is not likely to be due simply to their not being able to see the track clearly. This agrees with previous studies (Jones and De Jong, 1971).

Another difference between the Control and Parkinsonian subjects appeared on the sweep conditions, in the ability to keep in rhythm with the target, even where the amplitude was not matched. Most of the Parkinsonian subjects broke down completely once the frequency reached 1·0 Hz, while the Controls managed to generate a movement of some kind beyond the 1·5 Hz point where they reduced the amplitude of response below two-thirds of the target amplitude. Thus for normals, the average point of de-synchrony occurred where each movement (half-cycle) took about 338 ms (the one-third-of-a-second duration where movements become ballistic in normals), but the point of complete break-down only occurred where each movement took 289 ms. This is about the duration where individual aimed movements at this amplitude become wildly inaccurate (Flowers, 1976, fig. 13). Control subjects can therefore generate continuous action of roughly the right frequency well beyond the rate at which individual movements are too fast to be corrected during their progress. Presumably with practice the accuracy can be improved until it approaches the highly-skilled performance of the other studies cited above. The point of break-down in the Parkinsonian Group, however, is only marginally beyond the point of de-synchrony for these patients (450 as against 476 ms per movement) and this also corresponds to the duration at which aimed individual movements become grossly inaccurate (Flowers, 1976, fig. 13). It is only 50 ms faster for each movement than the average duration of movements executed 'open-loop'; that is, with visual information removed while the arm is in motion.

For the Controls, spontaneous generation of movement from information stored internally rather than directly from the display allows subjects to reduce their time-lag and to produce a smooth rather than jerky action, so that they come to match the target motion instead of following it. It also allows them to keep up with higher frequencies of movement than it is possible to follow directly. The evidence presented here suggests that Parkinsonian patients have lost at least two of these advantages. Their matching of the target is less good at all frequencies than the Controls, and they cannot continue when the target frequency reaches the point where movements become ballistic. They do, however, show evidence of reduced tracking lag on the regular tracks compared with their lag on the irregular ones, and their over-all lag is somewhat less on the noise condition than their previously measured RT for individual movements. Since the latter is also true of the Controls, it is clear that even the 'noise' task allows subjects to use some short-term predictive element in their tracking (Cassell *et al.*, 1973) exploiting the fact that the irregular motion is not entirely random (very high frequencies are not included as they make tracking impossible). The sine and ramp conditions allow even more for this kind of prediction, perhaps in the form of extrapolation from ongoing movements (Bartlett, 1951; Poulton, 1952). Parkinsonian patients may, therefore, have retained the ability to include some short-term prediction in their performance, although not to the same extent as the Controls. Maybe this is because the Controls can work from a more powerful long-term prediction of the over-all pattern of motion, which enables them to prepare their actions well in advance of events. (This also gives them another advantage, namely the ability to continue tracking appropriately over at least short periods independently of sensory input, as, for example, if the input is temporarily interrupted; an investigation of this is reported later.)

While the Parkinsonian subjects are less accurate in matching continuous movement at all frequencies, therefore, they appear to have particular difficulty in producing continuous movement of any kind, when this must be done spontaneously, or by 'internal' control with only infrequent corrective monitoring. As suggested by Stark (1968) they have lost the ability to control voluntary movements 'open-loop' and thus show the characteristics and limitations of a 'closed-loop' system. The deficit appears even at slow rates of movement, where the accuracy with which they can match a sinusoidal target motion is low, mirroring their clumsiness and lack of co-ordination in everyday life. But it appears even more acutely as the required speed of movement increases, and reaches a critical point where a series of movements must be generated more or less as a unit. That they cannot then produce a movement of any kind, even roughly accurate, suggests that these patients are deficient in some internal model of their own actions from which to generate movement spontaneously and to control it predictively.

SUMMARY

Subjects were tested on a pursuit tracking task using an oscilloscope display and joystick control. The target moved horizontally across the screen in three waveforms: a sine-wave of 125 mm amplitude, a constant-velocity ramp of 125 mm amplitude, and an irregular 'noise' pattern with a maximum amplitude of 110 mm. Results showed (1) RMS error scores for the 15 Parkinsonian subjects were greater than those of the 16 Control subjects at all frequencies of sine-wave (0·17–1·0 Hz), and at the highest frequency they approached the level where they were no better than holding the joystick still and not tracking at all. Error scores on the ramp track (0·11 Hz) were also greater than Control scores, but those for the irregular movement were not noticeably larger; (2) with cross-correlation analysis of subject and target movement, there was a greater average tracking lag in the Parkinsonian Group than in the Controls in all conditions; but even correcting for this, the error scores of the patients were still much greater, and still approached the 'do-nothing' level at the highest frequency; (3) Parkinsonian subjects, unlike Controls, showed little or no improvement in error score for the regular wave-forms as compared

with the irregular ones, indicating that they tend to track sine-waves as if they are unpredictable irregular tracks; (4) reducing the amplitude of the sine-wave to 80 or 40 mm did not lead to an improvement in tracking; the Parkinsonian error score was still greater than the 'do-nothing' level at 1·0 Hz. This, and the fact that as frequency increased on a sine-wave sweep these subjects lost synchrony with the target earlier than did the Controls (that is, at a lower frequency), indicates that they have particular difficulty in generating smooth continuous movement of all kinds, large or small, at more than a moderate rate.

These results are interpreted as suggesting that Parkinsonian subjects have, apart from their increased reaction time lag, a deficit in the strategy of movement. That is, they have difficulty in generating continuous regular movements spontaneously, and seem to lack a dynamic 'internal model' of their own movements from which to control them predictively.

ACKNOWLEDGEMENTS

The author would like to thank Dr. R. Langton Hewer for access to patients under his care, and Dr. M. Hilary Morgan for the clinical assessments, advice and encouragement. Also Mr. I. Low, Mr. M. Tajfel, Mr. P. Clark and Miss A. Griffiths for technical help; and Professor R. L. Gregory and colleagues for much helpful discussion. Financial support from the Medical Research Council is gratefully acknowledged.

REFERENCES

ANGEL, R. A., ALSTON, W. and HIGGINS, J. R. (1970) Control of movement in Parkinson's disease. *Brain*, **93**, 1-14.

BARTLETT, F. C. (1951) Anticipation in human performance. In: *Essays in Psychology Dedicated to David Katz*. Edited by G. Ekman, T. Husen, G. Johansson and C. I. Sandström. Uppsala: Almqvist and Wiksells.

BOWEN, F. P., HOEHN, M. M. and YAHR, M. D. (1962) Cerebral dominance in relation to tracking and tapping performance in patients with Parkinsonism. *Neurology, Minneapolis*, **22**, 32-39.

CASSELL, K. J. (1973) The usefulness of a temporal correlation technique in the assessment of human motor performance on a tracking device. *Medical and Biological Engineering*, **11**, 755-761.

—— SHAW, K. and STERN, G. (1973) A computerized tracking technique for the assessment of parkinsonian motor disabilities. *Brain*, **96**, 815-826.

EIDELBERG, E. and DUNMIRE, I. D. (1973) Linear systems analysis of motor control in Parkinsonism. In: *Proceedings of the Conference on Regulation and Control in Physiological Systems*. Pittsburgh, Pa: Instrument Society of America, pp. 239-240.

FLOWERS, K. A. (1975) Ballistic and corrective movements on an aiming task: intention tremor and parkinsonian movement disorders compared. *Neurology, Minneapolis*, **25**, 413-421.

—— (1976) Visual 'closed-loop' and 'open-loop' characteristics of voluntary movement in patients with parkinsonism and intention tremor. *Brain*, **99**, 261-310.

GREGORY, R. L. (1970) On how little information controls so much behaviour. *Ergonomics*, **13**, 25–35.

HORNE, D. J. DE L. (1973) Sensorimotor control in parkinsonism. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 742–746.

JONES, G. M. and DE JONG, J. D. (1971) Dynamic characteristics of saccadic eye movements in Parkinson's disease. *Experimental Neurology*, **31**, 17–31.

KELLEY, C. R. (1968) *Manual and Automatic Control.* New York: John Wiley.

MERRILL, W. J. and BENNETT, C. A. (1956) The application of temporal correlation techniques in psychology. *Journal of Applied Psychology*, **40**, 272–280.

NOBLE, M., FITTS, P. M. and WARREN, C. E. (1955) The frequency response of skilled subjects in a pursuit tracking task. *Journal of Experimental Psychology*, **49**, 249–256.

PERRET, E., EGGENBERGER, E. and SIEGFRIED, J. (1970) Simple and complex finger movement performance of patients with parkinsonism before and after a unilateral stereotaxic thalamatomy. *Journal of Neurology, Neurosurgery and Psychiatry*, **33**, 16–21.

POULTON, E. C. (1952) The basis of perceptual anticipation in tracking. *British Journal of Psychology*, **43**, 295–302.

—— (1974) *Tracking Skill and Manual Control.* New York: Academic Press, Chapter 3.

SCHWAB, R. S., CHAFETZ, M. E. and WALKER, S. (1954) Control of two simultaneous voluntary motor acts in normals and in parkinsonism. *Archives of Neurology and Psychiatry, Chicago*, **72**, 591–598.

STARK, L. (1968) *Neurological Control Systems*. New York: Plenum Press, pp. 338–347.

(*Received November 16, 1976*)

Brain (1978), **101**, 35-52

LACK OF PREDICTION IN THE MOTOR BEHAVIOUR OF PARKINSONISM

by KENNETH FLOWERS[1]

(*From the MRC Brain and Perception Laboratory, University of Bristol Medical School, Bristol BS8 1TD*)

INTRODUCTION

A MAJOR component of normal skilled movement is prediction. In a previous paper (Flowers, 1978*a*) it was suggested that normal subjects use prediction as much as possible in controlling their behaviour, especially in perceptual-motor skills. Subjects were described as building an 'internal model' of the external world, from which they can generate predictive hypotheses of future events, and as using these predictions in the immediate control of behaviour (Gregory, 1970). They use sensory information to build up their model and to trigger off predictions, rather than to initiate responses directly (except where prediction is impossible). Working this way enables them to circumvent the handicap of their reaction time, and also to continue appropriate actions in the absence of sensory data—if their predictions are correct. Inaccurate predictions may lead subjects to make greater errors than would occur with a strategy of direct response to the sensory input. These characteristics were demonstrated in 16 subjects performing three simple pursuit tracking tasks.

This report describes the tracking behaviour of two groups of subjects with neurological disorders of movement (Parkinson's disease and intention tremor of various kinds), and investigates the degree to which they show predictive control in initiating and controlling their actions. Previous work with these patients has shown that Parkinson's disease affects the patient's ability to produce pre-programmed 'ballistic' movements when aiming at a stationary target point, and also to generate smooth continuous movement over a wide range of frequencies (Flowers, 1975, 1976, 1978*b*), suggesting that this may represent a lack of prediction in the control of the subject's own movements. Do these patients also lack the normal tendency to predict future events in the external world to which they must direct their actions? The tremor group, who have considerable difficulty in controlling their own movements, but who show a normal predictive element in their aiming, were tested as a comparison group. Two features of predictive control were investigated, the ability to continue appropriate actions when sensory information is temporarily removed (Experiments 1 and 2), and the tendency to prepare actions in advance (Experiment 3).

---

[1] Present address: Department of Psychology, The University, Hull HU6 7RX

EXPERIMENTS

(1) *Tracking through Gaps in Sensory Data* (*Ramp Pattern*)

In this experiment, subjects were required to track a target moving continuously across a screen in a regular pattern. The target was made to disappear for two-second intervals, and the operator's strategy during these 'data gaps' was recorded. Sometimes the target continued in the same direction throughout the data gap, and sometimes it reversed its direction. Where gaps occurred, therefore, subjects could only make consistently appropriate movements to stay close to the target if they could predict where it was going to move in the next few seconds. A definite change or continuation of the tracking action was required over a period of at least four normal reaction times. Twelve out of 16 normal subjects tested previously had shown a tendency for predictive control on this task, in that they produced a continuous movement in one direction or the other during the gaps (that is, they did not usually just stop or move the control lever at random during the gap period); after some practice their predictions were mostly accurate, and their tracking became more efficient than it would have been if based on a direct following strategy (Flowers, 1978*a*). In this study the normal subjects were regarded as a Control Group against which to measure the performance of the patients.

Method and apparatus. An oscilloscope display and joystick control were used for the tracking task. Details of these have been given elsewhere (Flowers, 1976, 1978*a*).

Data gaps were produced by z-modulation of the oscilloscope beam. They were triggered each time by the experimenter with a push-button switch, and were put in the appropriate test runs at one point in each cycle in a standard irregular sequence for each run. Only the target marker was blanked, the subject's response spot remaining visible all the time.

Tracking was recorded on a UV recorder (SE Laboratories (EMI) type 3005/DL) with three traces, one each for target and subject movement, and the third to indicate marker disappearance.

Subjects. The Parkinsonian Group comprised 10 subjects, 6 men and 4 women, all outpatients with two or more years' history of the disease. Their ages ranged from 39 to 75 years with a median of 63 and a mean of 62·2 years. None of them had more than a moderate degree of the classical parkinsonian symptoms (tremor, rigidity and bradykinesia) and none had any sensory loss. They were all mobile and socially independent. Three patients were still working, one was prematurely retired because of a speech difficulty and 6 were past retirement age.

There were 8 subjects in the Tremor Group, 2 men and one woman with intention tremor associated with multiple sclerosis, and 5 men with idiopathic or essential tremor, from which they had suffered for two years or more. Their ages ranged from 38 to 70 years with a median of 57 and a mean of 56·4 years. Two were confined to wheelchairs, and all had some degree of social disability. Three patients were still working, 3 were past retiring age, one was a housewife and one was retired early on a disability pension. All essential tremor patients had an anti-gravity resting tremor of 5–6 Hz which persisted during voluntary movement. The 3 subjects with multiple sclerosis showed a mild to moderate cerebellar action tremor on both sides, although often more marked on one side. All the subjects in this group complained of difficulties in holding their hands steady (as with a cup and saucer) and in fine manipulative tasks such as writing, typing, putting a key in a lock or using a screwdriver.

The 16 (paid) Control subjects were drawn from the cleaning and portering staff of the University, except for one who was a University lecturer (for Experiment 3 there were 2 additional men and one woman drawn from the non-academic staff of the University). Their ages ranged from 34 to 72 years with a median of 59·5 and a mean of 57·3 years.

Target movement. The target movement to be tracked was a constant velocity ramp which moved horizontally to left and right across the screen at a rate of 25 mm/s. Each cycle of fifteen seconds comprised a 'long' movement of 125 mm across the screen and back (lasting 5 s each) and a 'short' movement of 62·5 mm across the screen and back (taking 2·5 s each). This pattern is shown in fig. 1.

Procedure and instructions. Four patients in the Parkinsonian Group had had some experience of pursuit tracking tasks some months prior to tackling this test (four sessions or more); 2 patients had performed once before. The other 4 patients had not been tested previously; these were given half-an-hour's practice in tracking step, ramp and sine-wave forms before tackling the test patterns. The Tremor Group had all been tested on two sessions or more before this one, but 6 of them had not been seen for a year previously, and they were given a similar practice period before the test trials.

All patients were first shown four cycles or more of the target movement with instructions to watch its movement and try to work out its pattern; if necessary they were given some hints and leading questions (short of actually describing the pattern directly) to draw their attention to the long-short-long-short shape of the track, and up to four cycles more to watch. All the patients claimed within this time to see the pattern of target movement, but 3 subjects in each group failed to describe it clearly. These subjects were asked about the track at the end of each trial, but did not improve their description of it; they were not prompted any further after the initial attempts.

Subjects were then told to track the target circle with the marker spot, trying to keep the spot 'inside or as close to the circle as possible all the time' and were given an initial test run of four cycles lasting sixty seconds with the target visible all the time.

Subjects were then shown the target disappearing for two-second periods whilst in motion, and told 'when the target disappears from view you have to guess where it is moving, and move the spot where you think the target is. The target continues to move all the time during the gap; the only difference is that you cannot see it—like a car going behind a house or an aeroplane going out of sight behind a cloud. If you guess correctly your spot should still be near the target when it re-appears'. They were given a practice run with four gaps, two of each kind to be presented in the test runs. On three subsequent test runs the target was visible for an initial 'orientating' cycle, and was then blanked out for two-second periods at some point on each of the next four cycles. On two occasions the circle was blanked out when it reached point A in fig. 1A, that is, in the middle of the large amplitude section of the pattern ('middle' gaps); on the other two occasions it was blanked out at point B in fig. 1A, that is just before it reversed its direction on the small amplitude section of the pattern ('reversal' gaps). The target thus disappeared at about the same point on the screen every time, with the target always moving in the same direction at the same speed (that is, the sensory information was the same in all cases). But the correct movement to make during the gap was contingent on what point of the track had been reached; on half the occasions the correct action was to continue the movement in the same direction at the same speed, while on the other occasions the correct response was to stop at some point and begin a new movement in the opposite direction. On the fourth test run the target was blanked out at points A and B on every cycle, so the subject never saw the target at the 'choice point' in the centre of the screen after the initial orientating cycle. There were thus ten gaps at each point for each subject over all, two in each of three test runs and four in the last run. Subjects' records were examined for evidence of the ability to distinguish the two directions of target movement during the data gap, and to generate appropriate movements.

Analysis of results. When the target blanks out during a pursuit-tracking task, subjects may show one of several reactions. Until the target reappears, they may (1) continue to move in the same direction as at the moment when the gap started ('inertia' reaction—*see* fig. 1A and B); (2) stop, either immediately or after one reaction time or more ('stop' reaction—*see* fig. 1C); (3) move the stick to and fro at random, or with no apparent consistent direction or pattern of movement ('random' reaction—*see* fig. 1D); (4) move, or continue to move, according to some definite plan or principle—in this case at the 'reversal' gaps, reversing the direction of movement at some point, and then continuing in the new direction

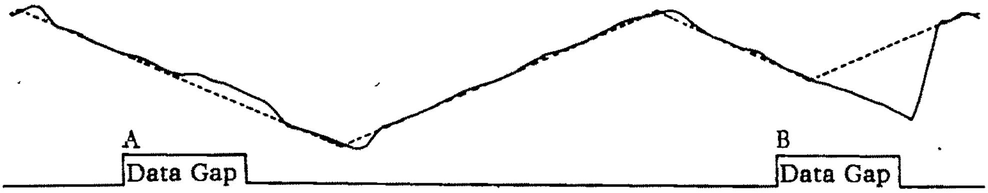


FIG. 1A, (Parkinsonian Subject 10), 'inertia' reactions. Dotted line = target. Continuous line = subject. The track runs from left to right 'Short' sections measure 62 mm in each direction, and take 2·5 s each. 'Long' sections measure 125 mm and last 5 s. The continuous line under the tracks indicates the occurrence of two-second data gaps, where the target disappears from view (while still moving). A = beginning of 'middle' data gap. B = beginning of 'reversal' data gap. In both cases this subject continues to move in the same direction throughout the gap as at the moment when the target disappeared. This reaction, which is the most common one found in Parkinsonian subjects, is correct for 'middle' gaps, but wrong for 'reversal' ones. In the latter case it generates a large error after two seconds which is quickly corrected when the target re-appears.

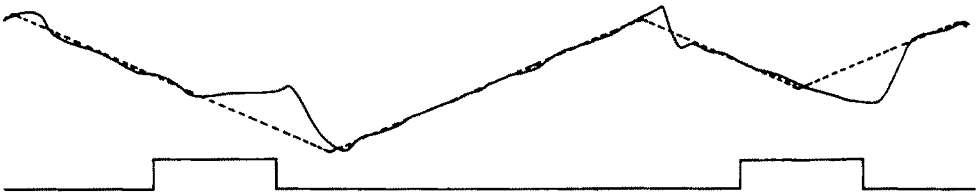


FIG. 1B, (Parkinsonian Subject 10), 'stop' reactions. Details of track as in fig. 1A. Another frequent reaction of these subjects during gaps is to stop, either after about one reaction time ('middle' gap) or gradually over a second or so ('reversal' gap).

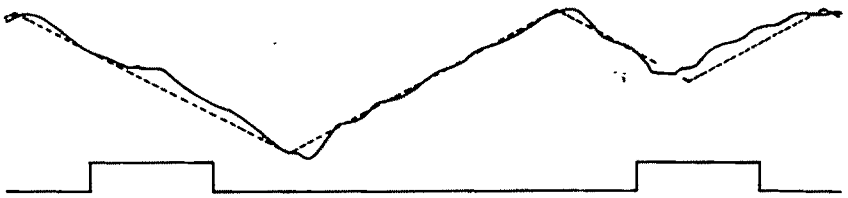


FIG. 1C, (Parkinsonian Subject 3), correct 'predictive' movements. Details of track as in fig. 1A. In these cases the subject makes the correct movements during the data gaps, albeit with a distinct pause before doing so.

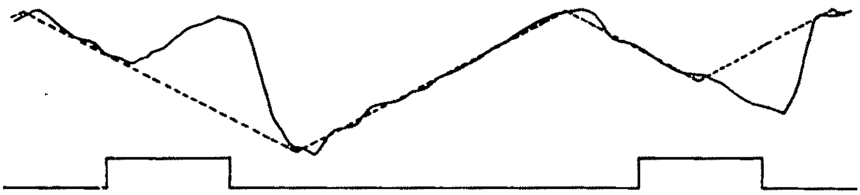


FIG. 1D, (Parkinsonian Subject 3), incorrect 'predictive' movements. Details of track as in fig 1A Often Parkinsonian prediction is not consistently appropriate. The same subject as in fig. 1C later guesses incorrectly which way the target is moving.

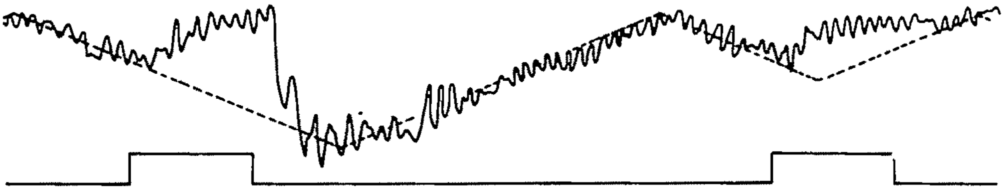


Fig. 1E, (Tremor Subject 6), 'reversal' reactions. Details of track as in fig 1A. The most common reaction in the Tremor Group is to reverse the direction of movement during the data gap. Here it is appropriate for the 'reversal' gap but not for the 'middle' one.

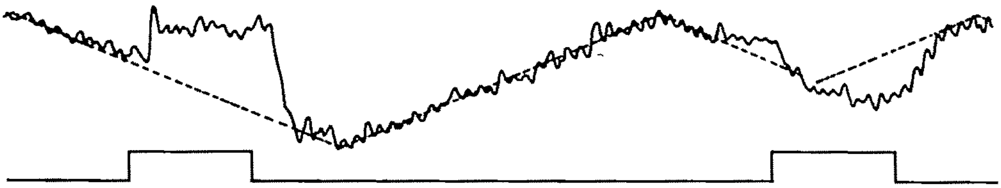


Fig. 1F, (Tremor Subject 6), 'stop' reactions. Details of track as in fig. 1A. Despite his severe tremor, this subject is able to match the ramp movement closely when it is visible. When the target disappears, a frequent reaction of this subject is simply to stop. Tremor subjects are better than Parkinsonian ones at predicting the target course with the target invisible, but not as good as normals.

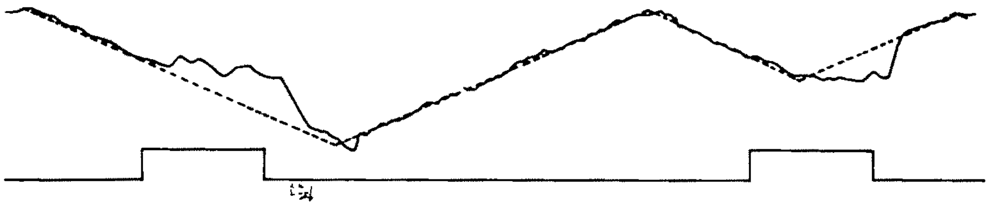


Fig 1G, (Tremor Subject 8), 'random' reactions. Details of track as in fig. 1A. Again this subject can follow the target movement very closely when it is visible, but shows signs of uncertainty in directing his movement when the target disappears, moving the spot to left and right more than once during the gaps. Even where they fail to predict, or predict wrongly, Tremor subjects rarely just drift on during gaps as Parkinsonian subjects do.

consistently until the target re-appears ('reversal' reaction—*see* fig. 1A and C); (5) move to the centre of the screen and stop there; (6) move towards the point, or in the direction, which is most probable from the past behaviour of target (i.e. extract some probability of future movement from past experience statistically); (7) reproduce the movement which was correct on the last occasion that the target was at this point—in this case therefore, making a response that was consistently wrong, not a random movement but an incorrect prediction (*see* fig. 1B).

Any of these strategies may be rational, its correctness contingent on the movement of the target. Subjects' movements were classified into these categories from the UV records. Examples of each category found here are shown in fig. 1. Mann-Whitney U-tests, two-tailed, were used to compare scores between groups.

TABLE 1. STRATEGIES OF MOVEMENT SHOWN BY 10 PARKINSONIAN AND 8 TREMOR PATIENTS DURING TWO-SECOND DATA GAPS: RAMP PATTERN

Subject			*All 20 gaps*								*Total correct (out of 20)*	*Last trial only (8 gaps)*								*Total correct (out of 8)*
			Middle gaps				*Reversal gaps*					*Middle gaps*				*Reversal gaps*				
No.	*Age*	*Sex*	‡1	2	3	4^{++}	$^{++}$1	2	3	4‡		‡1	2	3	4^{++}	$^{++}$1	2	3	4‡	
Parkinsonian Group																				
1 (P.T.)	56	M	10	0	0	0	2	0	0	8	18	4	0	0	0	1	0	0	3	7
2 (M W)	39	F	8	1	0	1	0	2	0	8	16	4	0	0	0	0	0	0	4	8
3 (E.W.)	75	F	7	1	1	1	5	1	0	4	11	2	1	0	1	2	0	0	2	4
4 (F H.)	59	M	10	0	0	0	9	0	0	1	11	4	0	0	0	4	0	0	0	4
5 (D.S.)	52	M	4	5	0	1	1	3	0	6	10	1	2	0	1	1	0	0	3	4
6 (A.S)	63	M	5	1	3	1	2	0	3	5	10	2	0	1	1	1	0	1	2	4
7 (V.W.)	74	F	6	3	1	0	3	2	2	3	9	1	2	1	0	1	1	1	1	2
8. (F W)	68	M	5	4	0	1	4	2	0	4	9	1	3	0	0	2	0	0	2	3
9. (I S.)	74	F	4	2	2	2	4	4	1	1	5	2	0	1	1	1	1	1	1	3
10 (N.B)	63	M	4	3	3	0	7	3	0	0	4	2	2	0	0	2	2	0	0	2
Median			5·5	1·5	0·5	1	3·5	2	0	4	10	2	0·5	0	0	1	0	0	2	4
Mean			6·3	2·0	1·0	0·7	3·7	1·7	0·6	4·0	10·30	2·3	1·0	0·3	0·4	1·5	0·4	0·3	1·8	4·10
(SD)			(2·4)	(1·7)	(1·3)	(0·7)	(2·8)	(1·4)	(1·1)	(2·8)	(4·27)	(1·3)	(1·1)	(0·5)	(0·5)	(1·1)	(0·7)	(0·5)	(1·3)	(1·97)
Tremor Group																				
1 (K M)	65	M	10	0	0	0	0	0	0	10	20	4	0	0	0	0	0	0	4	8
2 (R.C)	45	M	10	0	0	0	0	0	0	10	20	4	0	0	0	0	0	0	4	8
3 (H E)	70	M	10	0	0	0	1	1	0	8	18	4	0	0	0	0	0	0	4	8
4 (M.E.)	50	F	8	0	2	0	1	0	2	7	15	4	0	0	0	0	0	1	3	7
5. (E W)	63	M	7	1	1	1	0	3	0	7	14	3	0	0	1	0	0	0	4	7
6. (T P.)	51	M	9	0	0	1	4	1	0	5	14	4	0	0	0	2	1	0	1	5
7 (B.R.)	39	M	3	0	0	7	1	0	0	9	12	1	0	0	3	0	0	0	4	5
8. (K B)	68	M	3	1	4	2	1	3	3	3	6	1	1	2	0	0	1	2	1	2
Median			8·5	0	0	0·5	1	0·5	0	7	14·5	4	0	0	0	0	0	0	4	7
Mean.			7·5			1·4	1·0	1·0		7·4	14·88	3·1							3·1	6·25
(SD)			(3·0)			(2·4)	(1·3)	(1·3)		(2·5)	(4·64)	(1·4)							(1·4)	(2·12)
Control Group																				
Median.			9·5	0	0	0	0·5	0	0	8	18	4	0	0	0	0	0	0	4	8
Mean			7·9				1·9			6·9	14·81	3·4							3·1	6·44
(SD)			(3·1)				(2·9)			(3·9)	(6·52)	(1·4)							(1·6)	(2·61)

Category 1 = 'inertia', Category 2 = 'stop', Category 3 = 'random', Category 4 = 'reversal' reactions ‡ = correct or appropriate reaction $^{++}$ = false prediction error reaction
(Control data from Flowers, 1978*a*)

Results and discussion. As in the previous paper (Flowers, 1978*a*), all the subjects' movements during the gaps have been classified into Categories 1, 2, 3 or 4, since no examples of Category 5 were found; Category 6 is only applicable to 'noise' tracks, and Category 7 must be inferred from consistently inappropriate movements in Categories 1 and 4. The number of movements falling into each category for each subject are shown in Table 1, listing subjects in descending order of accuracy. It also includes the Control averages found previously in 16 normal subjects of roughly the same age and background.

In this Table, 'middle' gaps are those occurring in the middle of the large amplitude section of the track (*see* fig. 1A starting at A); and the appropriate response is to continue in the same direction throughout the gap (Category 1). 'Reversal' gaps are those occurring at the end of the small amplitude section of the track (starting at B), where the appropriate action is to reverse the movement and come back in the opposite direction (Category 4). As can be seen from the Table, the median number of correct actions in the Parkinsonian group is only ten out of twenty over-all, and on the final test run only four out of eight. Both these distributions are significantly worse than the Controls' (for all reactions: $U = 38$, $P < 0{\cdot}05$; for final run only: $U = 35$, $P < 0{\cdot}02$). Of the 10 subjects in the group only 2 showed a consistent ability to distinguish the correct movement in the two kinds of data gap. The predominant reaction in the other patients was Category 1, that is, to continue moving in the same direction throughout the gap as at the moment when the target disappeared—the 'inertia' response. They thus manage quite well on the 'middle' gaps, but rarely match the target movement on the 'corner' gaps (which means that their performance on the 'middle' gaps may be fortuitously good rather than deliberately so). Otherwise their reactions fall mostly into Categories 2 or 3 (suggesting that subjects are not producing any positive movement) rather than Category 4 (a false prediction).

The Tremor Group performance is not as good as that of the Controls (median correct movements 14·5 out of 20 over all and 7 out of 8 on the last trial), but this is due to a low score by 3 of the subjects, who made most of the errors in this group. As a whole the group did not differ from the Controls, and were better than the Parkinsonian patients (for all reactions: $U = 16{\cdot}5$, $P < 0{\cdot}05$; for final run only: $U = 17{\cdot}5$, which is not quite significant). Of the 3 subjects with low scores on the final run, one subject showed Category 1 errors on 'reversal' gaps and one subject showed the opposite, that is, Category 4 errors on 'middle' gaps. The other subject's reactions fell mostly into the 'uncertain' Categories 2 and 3. Where these subjects make errors, therefore, they tend to be false predictions of one kind or another more often than indecisive movements.

Although the two Parkinsonian subjects with the best (normal average) scores were among the youngest of these patients, there was no reliable correlation of performance with age in this group (Spearman $r_s = 0{\cdot}277$ n.s.). None of the subjects were notably deteriorated, and all were outwardly alert, orientated, mobile and (except one) cheerful. All of them could describe the task and instructions, and

6 of the 8 who scored badly had described the pattern correctly and outlined it on the table with a finger before they started. Most, too, were aware of their difficulty, making comments such as 'I lose it when it disappears' or 'I can't guess it if I can't see it.' That they often continued some movement during the gap, shows that they were not just distracted by the sudden disappearance of the target, or 'frozen' in their response. Rather it seems that they cannot generate continuous movement according to some internal 'model' of the external world, although they are able to follow a moving target when it is visible.

Three Parkinsonian and 2 Tremor patients who had not described the track pattern clearly before the test sessions, and who had scored badly on the test, were afterwards given a demonstration of the track with a direct description of it, and were then re-tested with data gaps. One of each group subsequently produced a more accurate performance (seven out of eight movements during gaps correct) but the others still made the same kind of errors as before.

(2) *Tracking through Gaps in Sensory Data: Sawtooth Tracks*

A similar test was carried out on the subjects of Experiment 1 with a sawtooth-shape track where, again, the subject had to make two distinctly different movements during gaps at different points on the track.

Method and apparatus. Subjects and instructions in this experiment were the same as in Experiment 1.

Target movement. The target moved from right to left across the centre of the screen at a rate of 31 mm/s for four seconds, and then returned in one steplike movement back to the starting point on the right for the next slow sweep across the screen. The track pattern is shown in fig. 2.

Procedure. Subjects were first shown four to six cycles of the track pattern and told to note the way it moved. Then, after a single eight-cycle practice run, two initial test runs were made with the target visible all the time, each of eight cycles (32 s). On the two subsequent test runs of sixteen cycles, gaps of two seconds each were put in at irregular intervals at each of two points on the track: (a) 'middle' gaps at point A in fig. 2A; that is, in the middle of the steady ramp movement to the left; and (b) 'corner' gaps at B in fig. 2A; that is, at the end of the ramp, so that the target jumped back to its starting point during the gap. There were four gaps of each kind in each sequence, making sixteen in all. Again, then, subjects had to make two distinctly different movements during different gaps; either a steady smooth movement in the same direction throughout the gap or a sudden forceful (ballistic) movement in the opposite direction at some point during the gap.

Analysis of results. The subjects' UV records were again examined to see if they could distinguish consistently between these two reactions. Movements made during each data gap were classified as in the previous experiment. Examples of the categories found in the performance of these subjects are shown in fig. 2.

Results and discussion. The pattern of this track is simpler than that of the ramp, and the distinction between the two required kinds of action during the data gaps clearer. But the Parkinsonian subjects still have the same difficulty in making appropriate movements although they all appeared to notice the characteristic shape of the track. Table 2 shows the scores for each patient on the two test sequences, listing them in the same order as for Experiment 1. The median Parkinsonian score of 9·5 out of 16 is significantly worse than the Controls

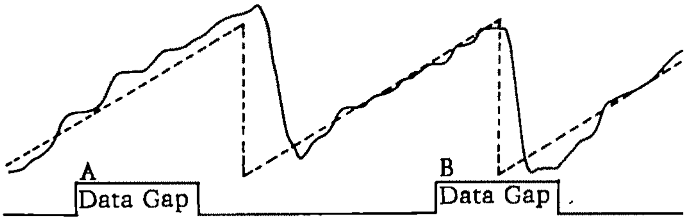


FIG. 2A, (Parkinsonian Subject 2), correct 'predictive' movements. Dotted line = target Continuous line = subject. The track runs from left to right. Each horizontal sweep measures 125 mm in extent and lasts four seconds. The continuous line under the track indicates the occurrence of two-second data gaps when the target disappears from view (while still moving). A = start of 'middle' gap. B = start of 'corner' gap. This subject manages to follow the movement of the target fairly closely through both kinds of data gap, distinguishing between the two different movements to do so. The record also shows a tendency for the subject to track by intermittent corrections rather than with a smooth constant velocity movement, whether the target is visible or not.

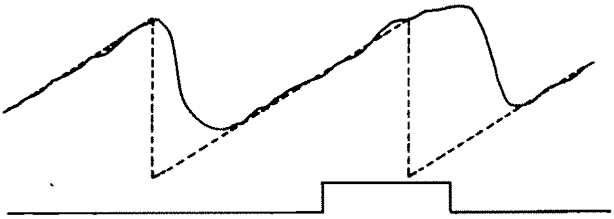


FIG 2B, (Parkinsonian Subject 10), 'inertia' reaction. Details of track as in fig. 2A On this track again, as on the ramp, the most common action during data gaps is to continue the ongoing movement through the whole of the data gap period, until the target re-appears. Most errors by this group, therefore, occur at 'corner' gaps, when a definite reversal of movement is required. This subject shows an intermittent tracking response in general, and the return movements at the end of the sweep are of the slow 'non-ballistic' kind typical of these patients.

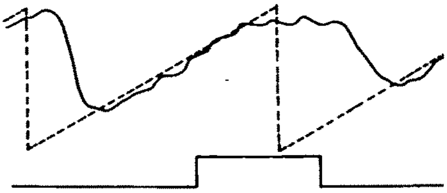


FIG. 2C, (Parkinsonian Subject 9), 'stop' reaction. Details of track as in fig. 2A. Here the subject waits at the point reached one to two reaction times after the start of the gap, until the target re-appears.

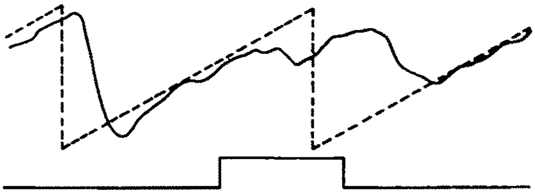


FIG 2D, (Parkinsonian Subject 9), 'random' reaction. Here the subject shows an indecisive pattern of movement, changing direction several times during the data gap.

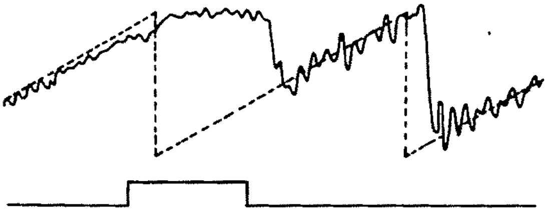


FIG 2E, (Tremor Subject 6), 'stop' reaction. Details of track as in fig. 2A. In this group, too, most of the errors occurred at 'corner' gaps, with the most common error being the tendency to stop moving until the target re-appears. When following the visible target, return movements are ballistic as in normals.

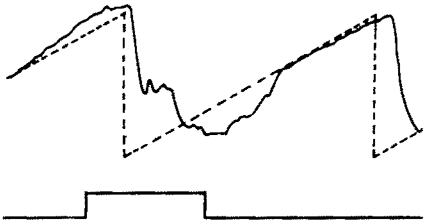


FIG. 2F, (Tremor Subject 8), interrupted ballistic movement. Details of track as in fig 2A. Occasionally Tremor subjects make a movement of the right kind, but not of the right amplitude (as with their aiming movements at a stationary target). When the target re-appears, their tracking performance returns to normal, albeit with a superimposed tremor.

($U = 35{\cdot}5$, $P < 0{\cdot}02$). Again most of the errors occur on the 'corner' gaps where a positive reversal of the movement is required. The most frequent error here is the 'inertia' reaction, continuing the movement until the target re-appears. Almost all the rest fall into Categories 2 and 3. The Tremor Group have about the same score as on the ramp (median 12·5 out of 16) which is not significantly different from the Controls ($U = 44$, n.s.) but which is not decisively better than the Parkinsonian Group either ($U = 24{\cdot}5$, n.s.). Errors are evenly spread between the categories, with relatively few in Categories 1 and 2 in contrast to the Parkinsonian Group.

Many of the Parkinsonian subjects show an intermittent following response with the target visible, as if working in an error-correcting mode all the time, and their return movements show the slow, non-ballistic characteristic found in previous experiments (Flowers, 1975, 1976), especially in those return movements made with the target invisible. The Tremor subjects, on the other hand, mostly produce typical ballistic return movements, and their general tracking performance shows evidence (apart from the high-frequency tremor) of a rate-matching type of movement for periods of a second or more (fig. 2).

TABLE 2. STRATEGIES OF MOVEMENT SHOWN BY 10 PARKINSONIAN AND 8 TREMOR PATIENTS DURING TWO-SECOND DATA GAPS: SAWTOOTH PATTERN

	First Trial								*Total correct (out of 8)*	*Second trial*								*Total correct (out of 8)*	*Grand total correct (out of 16)*
	Middle Gaps				*Reversal Gaps*					*Middle Gaps*				*Reversal Gaps*					
Subject No	‡1	2	3	4++	++1	2	3	4‡		‡1	2	3	4++	++1	2	3	4‡		
Parkinsonian Group																			
1. (P.T.)	4	0	0	0	0	0	0	4	8	4	0	0	0	0	0	0	4	8	16
2 (M W)	4	0	0	0	0	0	0	4	8	3	0	0	1	0	0	0	4	7	15
3 (E W)	4	0	0	0	1	0	0	3	7	4	0	0	0	0	0	0	4	8	15
4 (F H.)	3	1	0	0	0	1	1	2	5	3	0	1	0	1	0	2	1	4	9
5 (D.S.)	4	0	0	0	0	1	1	2	6	3	0	0	1	0	2	0	2	5	11
6. (A S)	2	0	0	2	2	0	1	1	3	4	0	0	0	4	0	0	0	4	7
7 (V.W.)	2	2	0	0	2	0	1	1	3	2	1	1	0	0	0	2	2	4	7
8 (F.W.)	2	1	1	0	0	0	0	4	6	1	0	3	0	0	0	1	3	4	10
9. (I S)	4	0	0	0	1	2	1	0	4	4	0	0	0	0	2	1	1	5	9
10 (N.B)	4	0	0	0	1	0	1	2	6	3	1	0	0	2	0	2	0	3	9
Median	4	0	0	0	0·5	0	1	2	6	3	0	0	0	0	0	0·5	2	4·5	9·5
Mean.	3·3				0·7		0·6	2·3	5·6	3·1						0·8	2·1	5·2	10·80
(SD)	(0·9)				(0·8)		(0·5)	(1·4)	(1·8)	(1·0)						(0·8)	(1·6)	(1·8)	(3·36)
Tremor Group																			
1 (K B.)	1	0	1	2	1	1	0	2	3	2	0	0	2	0	0	1	3	5	8
2. (R.C)	4	0	0	0	0	0	0	4	8	4	0	0	0	0	0	0	4	8	16
3 (H E.)	4	0	0	0	0	0	0	4	8	4	0	0	0	0	0	0	4	8	16
4 (M E.)	4	0	0	0	0	0	1	3	7	4	0	0	0	0	0	0	4	8	15
5 (E.W)	3	0	0	1	0	0	1	3	6	3	0	0	1	0	0	0	4	7	13
6. (T P)	2	2	0	0	0	2	0	2	4	2	1	1	0	0	0	0	4	6	10
7 (B R)	4	0	0	0	0	0	1	3	7	4	0	0	0	0	0	3	1	5	12
8. (K.B)	3	0	1	0	0	0	2	2	5	4	0	0	0	0	0	2	2	6	11
Median·	3·5	0	0	0	0	0	0·5	3	6·5	4	0	0	0	0	0	0	4	6·5	12·5
Mean:	3·1						0·6	2·9	6·0	3·4							3·3	6·6	12·63
(SD)	(1·1)						(0·6)	(0·8)	(1·9)	(0·9)							(1·2)	(1·3)	(2·92)
Control Group																			
Median·	4	0	0	0	0	0	0	4	7	4	0	0	0	0	0	0	4	8	15
Mean	3·3							3·4	6·81	3·4							3·9	7·31	14·13
(SD)	(1·3)							(0·8)	(1·52)	(1·2)							(0·3)	(1·40)	(2·66)

Category 1 = 'inertia', Category 2 = 'stop', Category 3 = 'random', Category 4 = 'reversal' reactions ‡ = correct or appropriate reaction ++ = false prediction error reaction
(Control data from Flowers, 1978*a*)

(3) *Surprise Steps*

Subjects performing an acquisition tracking task, where the target jumps from point to point on the display, appear at first sight to be following the target in an error-correcting mode very like a closed-loop servo-mechanism. It is not difficult, however, to show that they are in fact predicting the movement, if the target is moving according to an identifiable sequence. If the sequence is changed so that an unexpected jump occurs, many normal subjects will make entirely the wrong response altogether; otherwise their actions may show reliable evidence of being different from those that went before. This was found previously with the Control Group. The two Patient Groups were tested similarly to see how they compared.

Method and apparatus. These were the same as in the previous experiments.

Subjects. These were the same as before except that one Parkinsonian patient was not tested on this condition.

Target movement. The target moved in a step function from the centre of the screen alternately out to points 80 mm to the left or right, and back again, staying at each point for about three seconds. The sequence of movement was thus centre-left-centre-right-centre . . . etc. in discrete jumps. This is shown in fig. 3.

Instructions. Subjects were told to track the target circle with the marker spot, acquiring it as quickly as possible when it jumped, and then keeping the spot inside the circle until it moved again. They were not encouraged to anticipate the jumps, nor were they specifically told that the target movement was a simple pattern, nor that there would be an unexpected target movement at any point (this was checked by asking subjects afterwards whether they were surprised at the first 'false jump'—all said they were).

Procedure. There was no practice run as such, but each subject performed for between nine and twelve cycles after they had settled down and begun to acquire the target reasonably quickly (this always took place within two cycles). They were then presented with a 'false jump' where the target moved to the right when, according to the sequence, it should have moved to the left after returning to the centre point. This was followed by another jump to the right and back, and then a 'regular' cycle (to left and right), after which another 'false jump' to the right occurred. The next cycle was regular; on the next a third 'false' move was made; and finally came a last regular cycle.

Analysis of Results. Reaction times for the start of each acquisition movement were measured off the UV recorder traces to the nearest 10 ms. Two-tailed t-tests were used to compare reaction times at different points in the sequence.

Results and discussion. Mean reaction times, together with their standard deviations, for the cycle prior to the first false jump and onwards, are given in fig. 4 for the Parkinsonian Group and fig. 5 for the Tremor Group. Fig. 4 shows that the mean Parkinsonian reaction time for outward jumps just prior to FJ1 is some 10–20 ms faster than that found to initiate a move in previous studies with a step-tracking task. Reaction times for return movements are some 25–30 ms faster still. In these respects the Parkinsonian subjects resemble Controls, although their decrease in RT latency is somewhat less than normal. At the first 'false jump', however, only 3 of the 9 patients show any sign of moving in the wrong (predicted) direction rather than following in the correct but unexpected one. Of these 3 cases, moreover, one is dubious, the movement being very short in both amplitude and duration (*see* fig. 3C, D). The duration of all these false moves is much shorter than

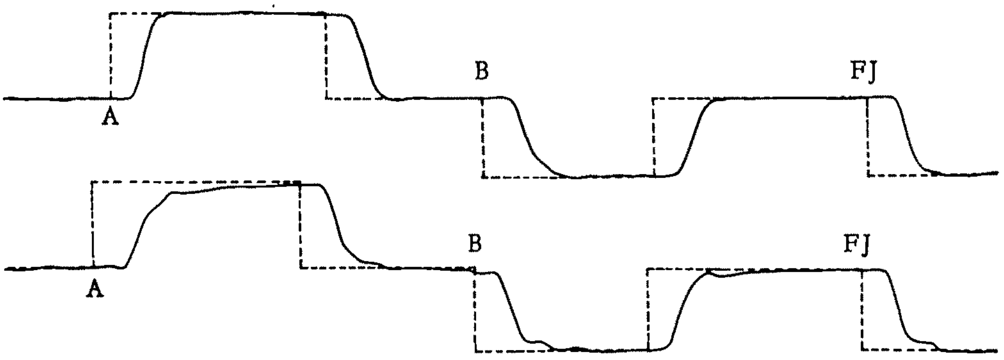


FIG. 3A and 3B, (Parkinsonian Subjects 10 and 2), movement in unexpected (correct) direction. Dotted line = target Continuous line = subject. The track runs from left to right. Each jump lasts about 3 s, and measures 80 mm in amplitude on the screen. A = outward move to left on cycle prior to first 'false jump'. B = outward move to right on cycle prior to first 'false jump' FJ = 'false jump', where the target moves to the right, when according to the cycle it would be expected to move to the left. Most Parkinsonian subjects follow the actual (unexpected) target direction at FJ, without any notable increase in reaction time at this point, indicating that they are probably not predicting the target movement as normals do.

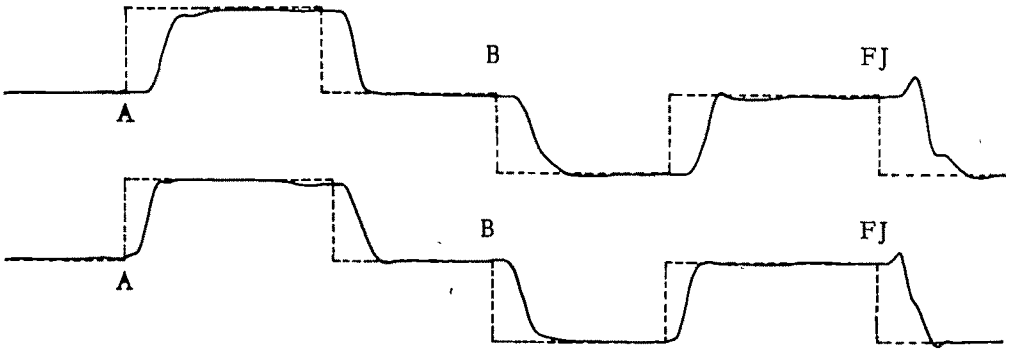


FIG. 3C and 3D, (Parkinsonian Subjects 8 and 3), movement in predicted (but wrong) direction. Details of track as in fig 3A. These subjects show an initial move in the wrong direction, similar to that found in many normals The movement in the expected-but-wrong direction is very short and quickly corrected, however, in contrast to the usual rather long reaction time shown by these patients to initiate movements to acquire a target

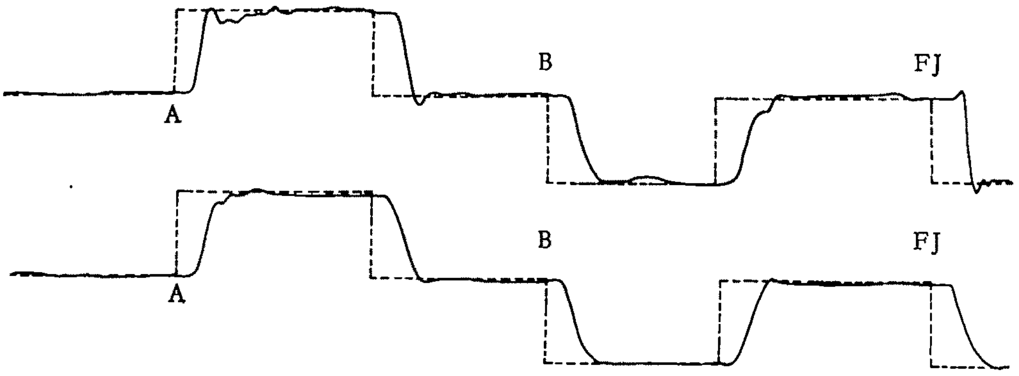


FIG. 3E and 3F, (Tremor Subjects 7 and 5), incorrect and correct movements. Details of tracks as in fig 3A The first subject makes an incorrect move at FJ, quickly corrects it and then acquires the target in the normal way The second subject makes a correct move at FJ, but only after a reaction time somewhat longer than on previous cycles.

their usual reaction time, and shorter even than the correction time for normals. The other 6 patients in this group respond in the unexpected direction with a reaction time only some 30 ms slower on average than that for the outward movements of the previous cycle (*see* fig. 3A, B and fig. 4). Although this increase in the 'true' reaction time is statistically significant (*see* fig. 4), the maximum increase compared to the previous cycle is only 50 ms.

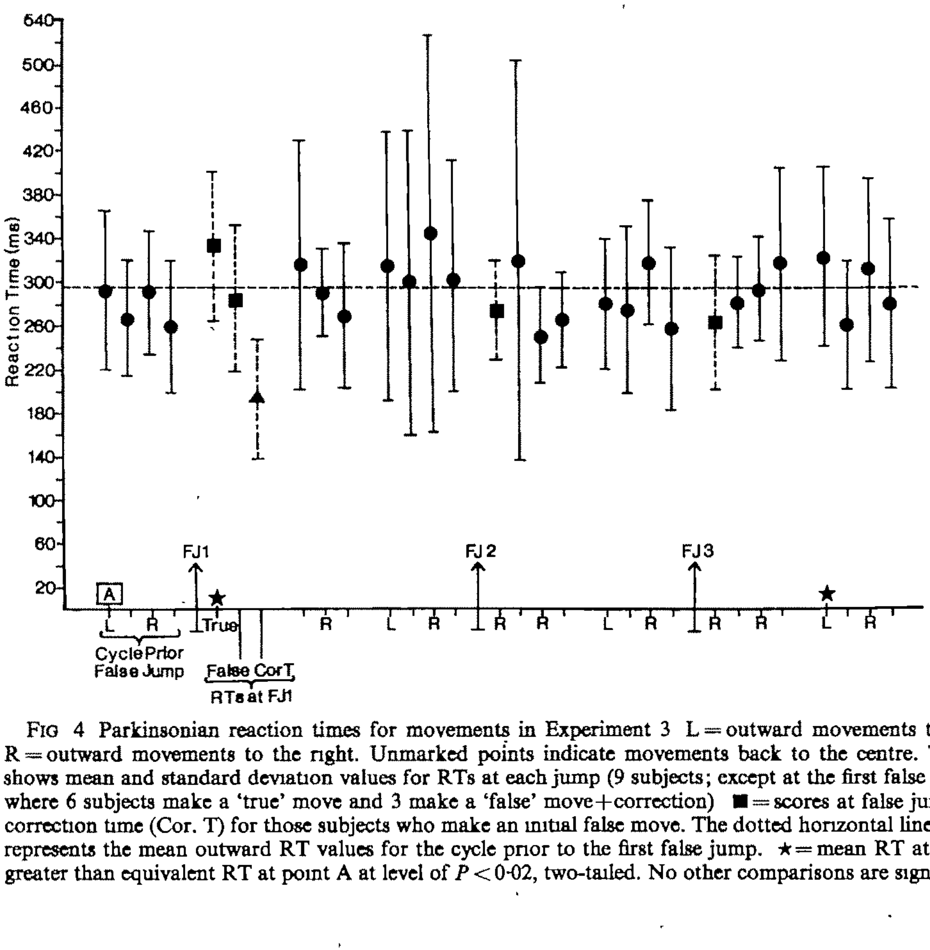


FIG 4 Parkinsonian reaction times for movements in Experiment 3 L = outward movements to the left R = outward movements to the right. Unmarked points indicate movements back to the centre. The graph shows mean and standard deviation values for RTs at each jump (9 subjects; except at the first false jump FJ1, where 6 subjects make a 'true' move and 3 make a 'false' move+correction) ■ = scores at false jumps. ▲ = correction time (Cor. T) for those subjects who make an initial false move. The dotted horizontal line at 295 ms represents the mean outward RT values for the cycle prior to the first false jump. ★ = mean RT at this point greater than equivalent RT at point A at level of $P < 0{\cdot}02$, two-tailed. No other comparisons are significant

After this initial surprise step, there is no general increase in mean reaction time to outward jumps as occurred in the other groups, and the reaction times (RTs) of these patients at the second and third false jumps tend to be shorter than before (fig. 4). There is, in general, no evidence that these patients were caught by surprise as were normals at the points on the track where the sequence was changed; although this makes the Parkinsonian Group appear superior to the controls in their tracking, it really indicates that they lack the normal tendency to predict events and to respond according to these predictions.

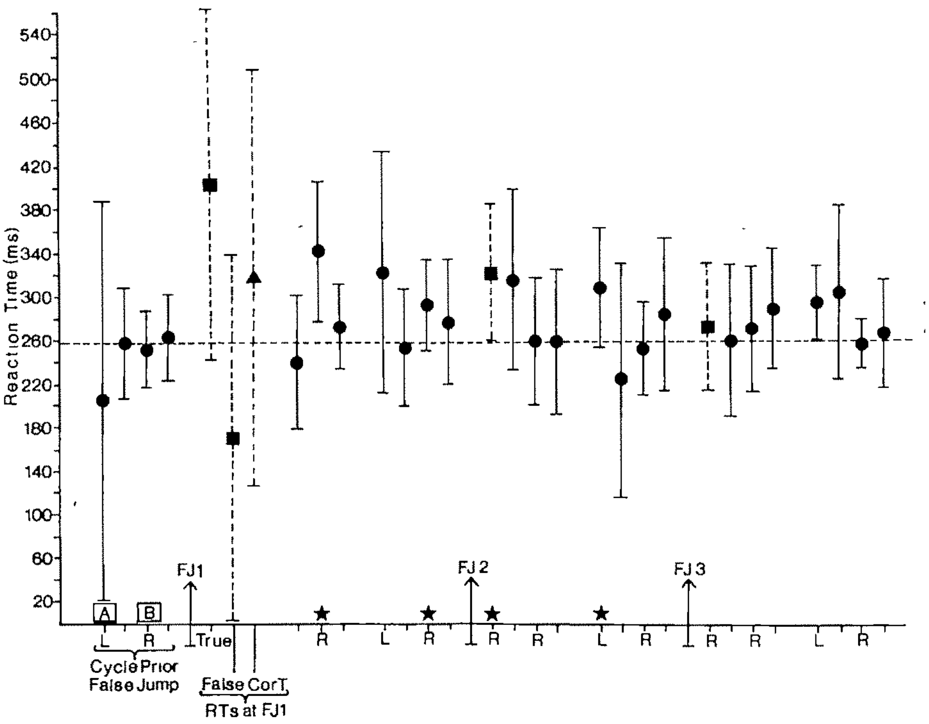


FIG. 5. Tremor reaction times for movements in Experiment 3 L = outward movements to the left. R = outward movements to the right. Unmarked points indicate movements back to the centre. The graph shows mean and standard deviation values for RTs at each jump (8 subjects; except at the first false jump FJ1, where 4 subjects make a 'true' move and 4 make a 'false' move+correction) ■ = scores at false jumps. ▲ = correction time (Cor. T) for those subjects who make an initial false move. The dotted line at 260 ms represents the largest mean outward RT values for the cycle prior to the first false jump. ★ = mean RT at this point greater than equivalent RT at points A or B at level of $P < 0{\cdot}05$, two-tailed, or better

The Tremor Group perform much more like the Control subjects on this condition (fig. 5). Their initial reaction time is on average some 40 ms faster than that for initiating aiming movements; half of them make a distinct move in the wrong direction at the first 'false jump' (fig. 3E) and correct it about one reaction time later; and the remaining 4 subjects make a correct move at FJ1 only after a reaction time which is some 140 ms longer than before (with only 4 subjects this is not quite significant statistically.) Subsequent RTs for outward jumps are increased compared with the pre-surprise level, gradually returning to about that level by about the third false jump cycle. Their performance shows more of the surprise element, therefore, and evidence of prediction in the initiation of movements.

DISCUSSION

In all three tests described here, Parkinsonian patients appeared not to show the normal tendency to predict the immediate future movement of the target they were tracking. On the pursuit tasks they failed to match consistently the direction of target movement during the data gaps, and on the acquisition task they were not caught by surprise when the sequence was interrupted by an irregular target movement. Since performance was measured in terms of the intention shown by the subject, rather than by the accuracy or speed of carrying out the intention, this 'deficit' or abnormal characteristic cannot simply be the result of the patients' difficulties in controlling their own movements. It was the subjects' general strategy of action that was abnormal, rather than their control of individual movements.

The well-known parkinsonian long reaction time, for instance, is irrelevant here, since the data gaps of Experiments 1 and 2 lasted for two seconds each, extending for at least 6 RTs of 320 ms. This duration allowed plenty of time for subjects to decide on and initiate a course of action if they were capable of it. And in fact the most common reaction was not just to stop or 'idle' during gaps, but to continue ongoing movement until the target re-appeared. On the acquisition task, moreover, it was the direction of movement, and its time for initiation compared with previous movements, which were important, and in both these features the Parkinsonian patients matched the movement of the target better than the other subjects, when this went against prediction.

For the same reasons, too, it seems unlikely that the Parkinsonian subjects were not able to watch and work out the pattern they were tracking because they had to concentrate all their attention on controlling the spot. Also, the Tremor Group did not show a lack of prediction, although their difficulties in controlling their own movements must have been at least as great as those of the Parkinsonian Group. And all the patients had plenty of opportunity to learn the track patterns, with at least four cycles of preview before starting to track, instructions to learn the pattern, and at least fifty per cent more practice trials with data gaps before testing than the Controls. Most subjects, in fact, described the patterns correctly at this stage. As a whole, too, the Parkinsonian Group had had as much general tracking experience as the Controls.

These results, then, suggest that Parkinsonian patients do not spontaneously use prediction as readily as normals in controlling their actions, but tend to be tied more directly to current sensory information, responding to events rather than anticipating them. Where the Tremor Group make errors, on the other hand, these tend to be wrong predictions, errors of commission rather than of omission, indicating that these subjects are at least as eager as normals to anticipate the future. The predominant reaction of 'inertia' or drifting shown by the Parkinsonian patients indicates a lack of positive prediction, although it may indicate that they are still capable of short-term extrapolation of movement such as is often found in normals on irregular tracks where useful prediction from a model is impossible; this would agree with previous findings on the parkinsonian tracking of linear and sinusoidal movement (Flowers, 1978*a*). In other words, these patients may have retained Bartlett's type B anticipation, but lost type C (Bartlett, 1951). It is this latter kind of anticipation which requires generation of a definite prediction of future events and which must be based on an 'internal model' of ongoing events (in this case the track pattern). It is the only kind of anticipation enabling operators to work independently of sensory information for any length of time and to any great advantage (Flowers, 1978*a*).

If this inference is correct, the parkinsonian deficit in tracking may be part of, or related to, the patient's akinesia which is characterized by lack of spontaneous action or speech. The subjects tested here were not outwardly deteriorated, but may still have had a degree of akinesia latent in them, which showed up on these tasks. Since they all claimed to 'see' the track patterns, and most described them correctly, their difficulty may be in using their knowledge to generate purposeful movement, that is, a kind of 'apraxia'. Alternatively their deficit may lie in the process of forming a model, that is, a high-level perceptual or 'agnosic' problem. Future work is designed to try to distinguish between these possibilities, testing parkinsonian patients on tasks of constructional apraxia, and on a test of perceptual analysis (Gottschaldt hidden figures).

SUMMARY

Three simple demonstrations of prediction in tracking suggest that, when tracking a moving target, normal subjects do not simply follow it from moment to moment, but usually try to predict its future course. Their actions are thus directed, at least partly, towards its expected future movement. These three tests were given to 10 subjects suffering from Parkinson's disease. The results suggest that prediction is not as important a factor in their performance as it is in normals. Eight patients with intention or cerebellar tremor showed a greater degree of prediction in their tracking behaviour, although this was not always as accurate as that of the controls.

ACKNOWLEDGEMENTS

The author would like to thank Dr. R Langton Hewer for access to patients under his care, and Dr. M. Hilary Morgan for clinical assessments, advice and encouragement. Also Mr. I. Low, Mr. A. P. W. Makepeace, Mr. P. Clark and Miss A. Griffiths for technical help; and Professor R. L. Gregory and colleagues for much helpful discussion. Financial support from the Medical Research Council is gratefully acknowledged.

REFERENCES

BARTLETT, F. C. (1951) Anticipation in human performance. In: *Essays in Psychology Dedicated to David Katz.* Edited by G. Ekman, T. Husen, G. Johansson and C. I. Sandström. Uppsala: Almqvist and Wiksells.

—— (1958) *Thinking.* London: Allen and Unwin, chapter 1.

FLOWERS, K. A. (1975) Ballistic and corrective movements on an aiming task: intention tremor and parkinsonian movement disorders compared. *Neurology, Minneapolis,* **25,** 413–421.

—— (1976) Visual 'closed-loop' and 'open-loop' characteristics of voluntary movements in patients with Parkinson's disease and intention tremor. *Brain,* **99,** 269–310.

—— (1978*a*) The predictive control of behaviour: Appropriate and inappropriate actions beyond the input in a tracking task. *Ergonomics.* In press.

—— (1978*b*) Some frequency response characteristics of parkinsonism on pursuit tracking. *Brain,* **101,** 19–34.

GREGORY, R. L. (1970) On how little information controls so much behaviour. *Ergonomics,* **13,** 25–35.

(*Received February 15, 1977*)

Brain (1978), **101**, 53-63

CARCINOMATOUS NEUROMUSCULAR SYNDROMES

A CLINICAL AND QUANTITATIVE ELECTROPHYSIOLOGICAL STUDY

by THOMAS PAUL, B. C. KATIYAR, SURENDRA MISRA *and*
G. C. PANT

(*From the Divisions of Medical Neurology and Radiotherapy, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India*)

INTRODUCTION

UNDER the heading of 'neuromyopathy', Brain and Henson (1958) described all the neurological syndromes associated with carcinoma. Croft and Wilkinson (1963) subsequently used this term for neuromuscular disorders where on clinical grounds alone it was impossible to define them into primarily muscular, or secondary to neural degeneration, or both. Shy and Silverstein (1965) retained this term to designate a definite clinical syndrome of symmetrical proximal muscle weakness and wasting with hyporeflexia. In these patients, the authors found histological evidences of myopathic or myopathic and neuropathic lesions. Although, in earlier studies, exact localization of the lower motor neuron lesion could not be obtained on clinical examination alone, it has now become possible, with the aid of neurophysiological and pathological techniques, to delineate these syndromes into neuropathy, myopathy, or neuromyopathy. On these grounds, McLeod (1975) disliked the term 'neuromyopathy' when referring to the non-metastatic neuromuscular syndromes of malignant lesions.

During recent years, the neuromuscular disorders have been studied electrophysiologically by various authors (Thage, Trojaberg and Buchthal, 1963; Moody, 1965; Trojaborg, Frantzen and Andersen, 1969; Campbell and Paty, 1974). In these studies, the incidence of abnormalities has varied from 29-70 per cent. It appears that a uniform picture has yet to emerge. Using quantitative electromyography and nerve conduction studies, and statistically evaluating the data against age-matched controls, the present study was undertaken to re-evaluate 'neuromyopathy' and other 'neuromuscular disorders'.

MATERIAL AND METHODS

The Patients

One hundred and seven males and 88 females with proven malignancies of various organs admitted to the wards or referred to us on account of neurological symptoms were examined. The mean age of the patients was 44·9 ± 10·7 years ($P > 0{\cdot}05$ of the controls). They were examined clinically for any motor dysfunction, presence of wasting and fasciculations, or reflex pattern and sensory abnormalities. The patients above the age of 65 years, and those taking neurotoxic drugs or alcohol or having other concomitant diseases such as diabetes, renal failure, hepatic, thyroid, or adrenal dysfunction, or nutritional deficiency, which are known to affect the nervous system, were excluded.

Electrophysiological Studies

Electrophysiological studies were done before the institution of treatment by radiotherapy, chemotherapy or surgery and were performed on a Medicor two-channel myograph (Budapest) at a constant room temperature of 27° C. The methods described by Cohen and Brumlik (1968) and Downie (1969) were used. Using the same concentric, co-axial electrode (TE1), four muscles were sampled in each patient, *viz.*, deltoid, thenar, gluteus maximus and extensor digitorum brevis. The analysis of motor unit potential duration and amplitude was done by the method of Skaria, Katiyar, Srivastava and Dube (1975).

Motor conduction velocities (McV) were measured in the median and peroneal nerves and the orthodromic sensory latency in the median nerve. Repetitive ulnar nerve stimulation at the wrist, to test for the fatiguability was done when indicated, by giving supramaximal surface stimuli at the frequencies of 1, 3 and 10 per second.

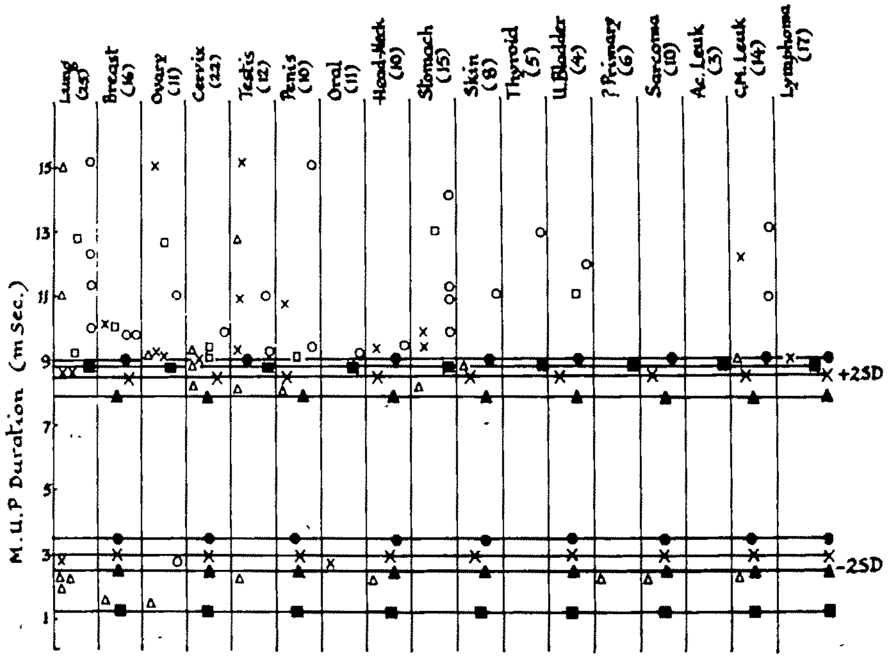


FIG. 1. Motor unit potential durations of the deltoid (△), thenar (×), gluteus maximus (□), and extensor digitorum brevis (○) muscles in patients with various malignancies. Only values beyond the mean ±2 SD of the controls are shown.

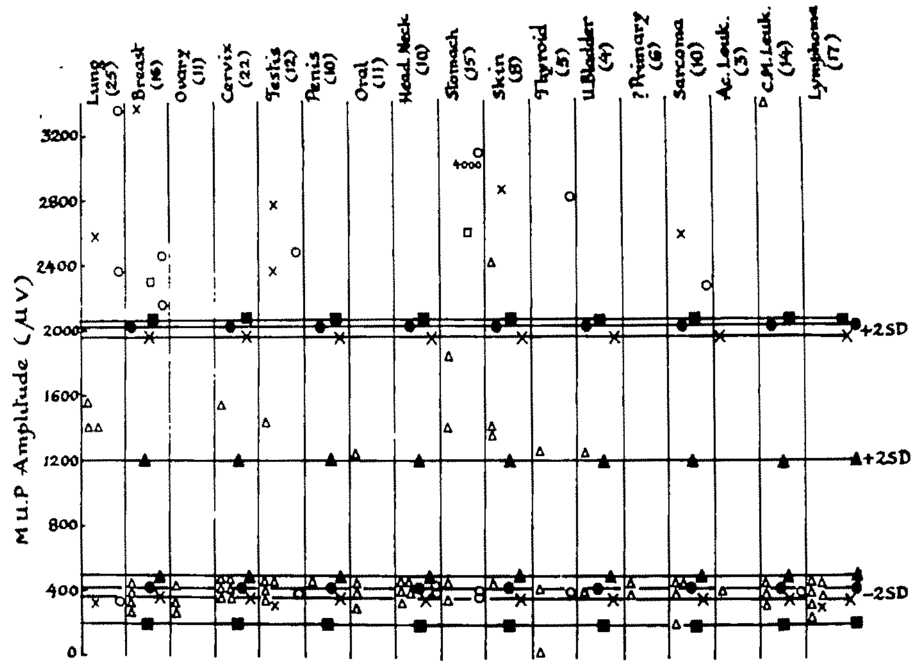


FIG. 2 The motor unit potential amplitude of the deltoid (△), thenar (×), gluteus maximus (□), and extensor digitorum brevis (○) muscles in patients with various malignancies. Only values beyond the mean ±2 SD of the controls are shown.

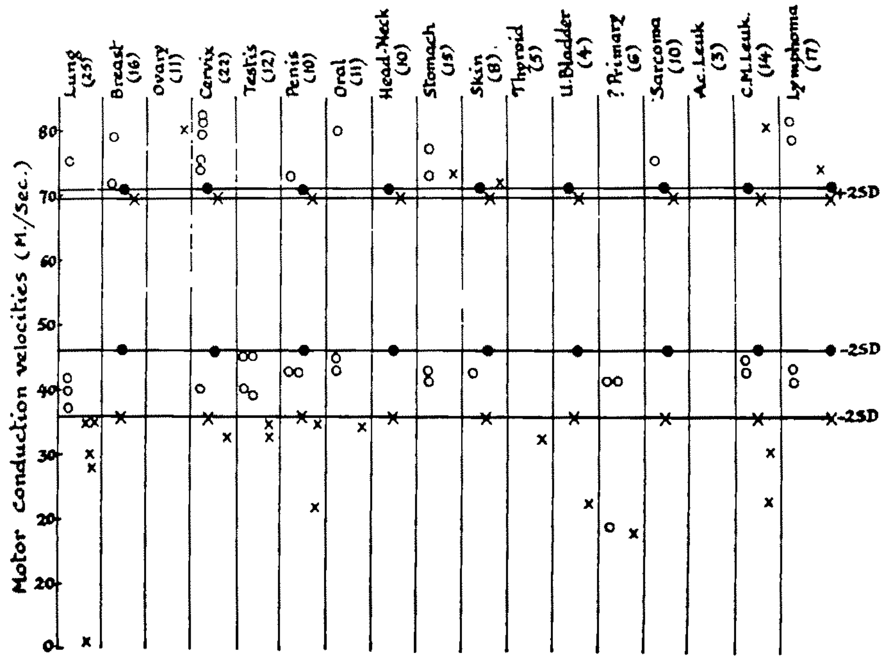


FIG. 3 Motor conduction velocities in the median (○), and peroneal nerves (×) in patients with various malignancies Only values beyond the mean ±2 SD of the controls are shown

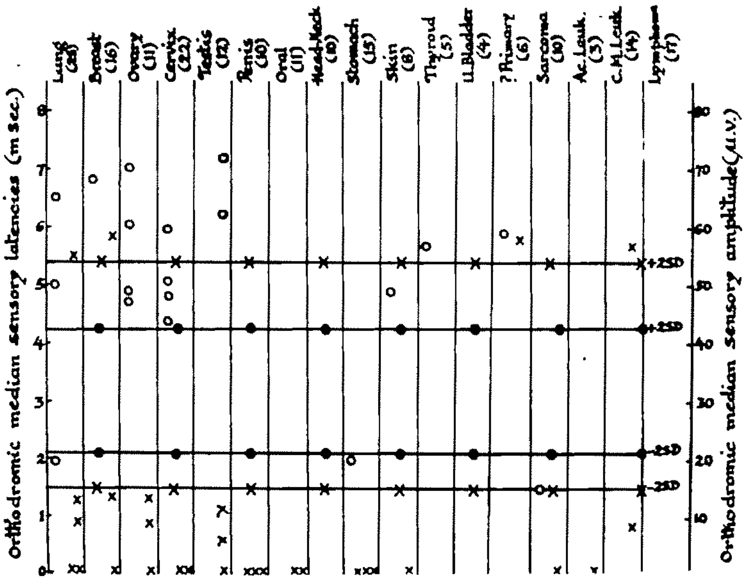


FIG. 4. Median nerve sensory latencies (O) and potential amplitudes (X) in patients with various malignancies Only values beyond the mean ±2 SD of the controls are shown.

Thirty male and 20 female healthy controls with a mean age of 40·9±14·1 years were also subjected to these studies. Their mean values for the motor unit potential duration and amplitude and the conduction velocities are shown in figs. 1–4. These parameters were compared with those obtained from the patients and were considered to be abnormal if the values were beyond the mean ±2 SD of the controls.

Interpretation of Results

The EMG abnormalities were classified in descriptive terms. Brief duration, small amplitude, overtly abundant motor unit potentials with increased polyphasic potentials were classified into 'BSAPP' pattern; those showing denervation potentials, often associated with significantly prolonged MUP duration, reduced interference pattern and increased polyphasic potentials were labelled as having a 'denervation pattern' (DN pattern), and the patients who showed denervation potentials in association with the BSAPP pattern were considered to have a 'mixed pattern'.

The nerve conduction abnormalities were classified into motor (MN), sensory (SN) and sensorimotor (SMN) neuropathy. Sensory neuropathy was considered if the median latency time was significantly prolonged, or the sensory evoked potentials could not be elicited, or their amplitudes were significantly reduced even in the presence of normal latency time.

RESULTS

Clinical Considerations

In the present study, the clinical incidence of non-metastatic neurological syndromes was 30 per cent, seen more often in bronchogenic carcinoma (48 per cent), ovarian tumours (46 per cent), and testicular tumours (42 per cent). These complications were found in about a third of the patients having malignancies of the breast, stomach or penis, and in about a fifth of the patients with malignancies at other sites (Table 1).

Neuromuscular involvement was the commonest and was observed in all malignancies except of the thyroid. Neuropathic symptoms in the form of tingling, numbness and paræsthesiæ were obtained in 29 patients (15 per cent). Objective sensory abnormalities, however, were noted in only 14 patients (7 per cent). One patient with bronchogenic carcinoma had motor neuropathy simulating Guillain-Barré syndrome.

Muscle weakness as a predominant sympton was seen in 7 patients. Difficulty in rising from the sitting position, climbing stairs, and weakness during walking were the usual complaints.

TABLE 1. INCIDENCE OF CLINICAL ABNORMALITIES IN VARIOUS MALIGNANCIES

	Muscle wasting				*Objective sensory abnormalities*		*Total incidence of abnormalities*	
	Proximal		*Generalized*					
Site (No.)	*No.*	*%*	*No.*	*%*	*No*	*%*	*No.*	*%*
Lung (25)	3	12	6	24	3	12	12	48
Cervix (22)	1	5	3	14	1	5	5	23
Lymphoma (17)	1	6	1	6	1	6	3	18
Breast (16)	2	13	2	13	1	6	5	31
Stomach (15)	0	0	4	27	1	7	5	33
Chr. myeloid leukæmia (14)	1	7	2	14	1	7	4	29
Testes (12)	1	8	2	16	1	8	5	42
Ovary (11)	1	9	3	27	1	9	5	46
Oral cavity (11)	1	9	1	9	1	9	3	27
Penis (10)	1	10	1	10	1	10	3	30
Head and neck (10)	0	0	1	10	0	0	2	20
Sarcoma (10)	1	10	0	0	0	0	2	20
Skin (8)	0	0	1	13	0	0	2	25
Thyroid (5)	0	0	0	0	0	0	0	0
Urinary bladder (4)	0	0	0	0	1	25	1	25
Ac. leukæmia (3)	0	0	0	0	0	0	0	0
Unknown primary (6)	1	17	1	17	1	17	2	33
Total	14	7	28	14	14	7	59	30

On clinical examination, muscle weakness and wasting were observed in 42 patients (22 per cent), and were associated with neuropathic symptoms in a half of them. Generalized wasting was more frequent and striking in 28 patients (14 per cent), whereas proximal wasting confined to the shoulder and pelvic girdle muscles was seen in only 14 patients (7 per cent). Weakness was generally mild except in 10 patients where it was severe. Two patients with generalized wasting had fasciculations. None of them had pain or tenderness of the muscles, suggesting polymyositis or dermatomyositis.

Hyporeflexia was seen in 23 (12 per cent) patients, 14 (7 per cent) with generalized and 9 (5 per cent) with proximal muscle involvement. The deep reflexes were absent in 2 patients.

Involvement of the central nervous system was seen in 7 (4 per cent) patients only and was frequent in bronchogenic carcinoma, where 5 (20 per cent) of the 25 patients showed various abnormalities—mental changes (3), cerebellar syndrome (2), and bulbar palsy, motor neuron disease and myelopathy (one patient each). A patient with testicular tumour and another with lymphoma had motor neuron disease and bulbar palsy, respectively.

Electromyographic Abnormalities

Electromyographic abnormalities were seen in 63 patients (32 per cent). The denervation pattern was the commonest and was seen in all the malignancies except acute leukæmia. Denervation potentials were seen in 34 patients, and in 18 of them were associated with prolonged MUP duration. Evidence of chronic denervation, that is prolonged MUP duration with reduced interference pattern and increased polyphasic activity, was found in the remaining 16 patients.

The BSAPP pattern was seen in 8 patients (4 per cent); 2 of them had bronchogenic carcinoma, and one patient each suffered from malignancy of the breast, ovary, head and neck, sarcoma, and acute and chronic leukæmia. The BSAPP pattern in conjunction with the denervation potentials was seen in 5 patients (3 per cent) with carcinoma of the oral cavity (2), lung, testes and unknown primary (one patient each) (Table 2).

Nerve Conduction Abnormalities

Abnormalities in nerve conduction were seen in patients with tumour at all sites except the head and neck, the over-all incidence being 26 per cent (Table 2). Sensory neuropathy was more frequent than motor or sensorimotor neuropathy and affected about a half of the patients with ovarian tumours and about a fifth of those with testicular or penile malignancies. Motor neuropathy, on the other hand, was more frequent in malignancies of the penis (20 per cent), lung (16 per cent) and chronic myeloid leukæmia (14 per cent). Sensorimotor neuropathy was common in testicular (20 per cent) and lung tumours (12 per cent).

Neuromuscular transmission studies were normal in all the patients investigated with repetitive nerve stimulation.

Clinico-electrophysiological Correlates

Of the 42 patients with muscle wasting, electromyographic (EMG) abnormalities were found in 36 (86 per cent) and NCV abnormalities in 15 (36 per cent)

TABLE 2. INCIDENCE OF ELECTROPHYSIOLOGICAL ABNORMALITIES IN VARIOUS MALIGNANCIES

	EMG				*NCV*				*Total*	
Malignancy (No.)	*BSAPP*	*DN*	*BSAPP + DN*	*Total*	*SN*	*MN*	*SMN*	*Total*	*No.*	*%**
Lung (25)	2	10	1	13	1	4	3	8	16	64
Cervix (22)	0	5	0	5	2	0	1	3	7	32
Lymphoma (17)	0	3	0	3	0	2	0	2	5	29
Breast (16)	1	3	0	4	2	0	0	2	5	31
Stomach (15)	0	5	0	5	2	1	1	4	7	47
Chr. myeloid leukæmia (14)	1	3	0	4	1	2	0	3	5	36
Testes (12)	0	5	1	6	2	1	3	6	7	58
Ovary (11)	1	4	0	5	5	0	0	5	7	64
Oral cavity (11)	0	2	2	4	1	1	1	3	5	46
Penis (10)	0	2	0	2	2	2	1	5	5	50
Head and neck (10)	1	1	0	2	0	0	0	0	2	20
Sarcoma (10)	1	1	0	2	1	0	0	1	2	20
Skin (8)	0	2	0	2	1	1	0	2	3	38
Thyroid (5)	0	1	0	1	0	0	1	1	1	20
Urinary bladder (4)	0	1	0	1	0	1	0	1	1	25
Ac. leukæmia (3)	1	0	0	1	1	0	0	1	1	33
Unknown primary (6)	0	2	1	3	0	1	2	3	3	50
Total (195)	8	50	5	63	21	16	13	50	82	
Percentage	4	26	3	32	11	8	7	26	42	

* Denotes the incidence of electrophysiological abnormalities occurring singly or in combination in patients with various malignancies.

patients. The neuropathies of the motor, sensory and mixed varieties were equally distributed with an incidence of 12 per cent (Table 3).

In patients with generalized wasting, the denervation pattern was seen in 75 per cent, 39 per cent of them having abnormalities in nerve conduction as well. These findings of generalized wasting point to a neuropathic ætiology. The BSAPP was seen in a single patient only. In patients with proximal wasting, on the other hand, the electromyographic patterns were variable. The BSAPP pattern was seen in 6 (43 per cent) patients, the denervation pattern in 4 (29 per cent) and the mixed pattern in another 4 (29 per cent) patients.

TABLE 3. INCIDENCE OF ELECTROPHYSIOLOGICAL ABNORMALITIES IN PATIENTS WITH AND WITHOUT MUSCLE WASTING

	EMG abnormalities						*NCV abnormalities*					
	DN		*BSAPP*		*BSAPP+DN*		*MN*		*SN*		*SMN*	
Patients (No.)	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Generalized wasting (28)	21	75	1	4	0	0	4	14	3	11	4	14
Proximal wasting (14)	4	29	6	43	4	29	1	7	2	14	1	7
Clinically normal (145)	25	17	1	1	1	1	11	8	15	10	8	6

Electrophysiological abnormalities may be present even before clinical abnormalities can be demonstrated by physical examination. Thus, of the 145 patients, EMG abnormalities were found in 27 patients (19 per cent) along with NCV abnormalities in 15 (10 per cent). Nineteen patients (16 per cent) showed only NCV abnormalities.

DISCUSSION

Proper electrophysiological evaluation of the carcinomatous neuromyopathies has been done in a few instances only and the results have often been variable. The present study, dealing with various malignancies, revealed clinical neuromuscular and electrophysiological abnormalities in 30 per cent and 42 per cent respectively. The abnormalities were frequently seen in malignancies of the lung, ovary, testes, penis, stomach and oral cavity, in that order. In a similar study of 82 patients, Moody (1965) found clinical abnormalities in 23 per cent and electrophysiological alterations in 29 per cent, more often with tumours of the lung and the stomach. Other studies relate only to lung tumours with an electrophysiological incidence varying from 47 per cent to 70 per cent (Thage *et al.*, 1963, Trojaborg *et al.*, 1969; Campbell and Paty, 1974).

Abnormalities in nerve conduction were found in 26 per cent of our patients. There was a slight preponderance of sensory neuropathy over motor or sensorimotor neuropathy. In the majority of patients, slowing of conduction velocity was mild, irrespective of the type of neuropathy. Usually sensory conduction is markedly impaired by comparison with motor conduction (McLeod, 1975). In contrast to our observations, Moody (1965) found a higher incidence of sensorimotor neuropathy (12 per cent). In patients with lung cancer, Trojaborg *et al.* (1969) found motor neuropathy only, while Campbell and Paty (1974) encountered mild peripheral neuropathy of the non-demyelinating type in 4 out of 26 patients and significant loss of motor and sensory nerve fibres in 9 patients. In spite of the mild slowing of velocities in general, which suggested predominantly an axonal lesion, Croft, Urich and Wilkinson (1967), in their histopathological study, observed abnormalities both in axons and myelin sheaths.

The Lambert-Eaton syndrome is probably rare and like Hildebrand and Cöers (1967) and Trojaborg *et al.* (1969), we did not observe it in any of our patients.

Electrophysiological correlates in our patients revealed certain interesting findings. The generalized wasting was neurogenic, as all the patients except one showed the denervation EMG pattern, along with NCV abnormalities in the majority. Generalized wasting, although recognized previously, has not been documented in electrophysiological terms. The proximal wasting, on the other hand, was 'myopathic', 'neuropathic' or 'neuromyopathic'. Six patients showed a BSAPP pattern while 8 of our 14 patients showed neuropathic features. Four had an exclusive denervation pattern and the others had denervation potentials in conjunction with the BSAPP pattern. The combination of denervation potentials with a BSAPP pattern is well recognized in proximal wasting. Shy and Silverstein (1965) found myopathic units in 16 of the 26 patients and 11 of them had evidence of denervation. These authors concluded that the electrophysiological observations in their patients with neuromyopathy point to a primary neuronal or axonal disorder. The proximal distribution of wasting in them, and the presence of myopathic potentials, do not sufficiently establish the diagnosis of primary muscle disorder. Our findings concur with these observations.

Application of electrophysiological techniques has greatly helped in unmasking latent neuromuscular involvement in cancer patients. This was possible in 46 of the 145 patients. Similar observations have been made by Moody (1965), Trojaborg *et al.* (1969) and Campbell and Paty (1974).

The pathogenesis of the various neuromuscular syndromes remains obscure. Factors like toxins, viral infections, and immunological mechanisms have been incriminated. In a country like India, where the majority of the population lives in conditions of sub-clinical nutritional deficiency and patients with malignant disease are grossly cachectic, nutritional factors may be important. Muscle wasting in chronic malnutrition and in association with other chronic diseases, like widespread malignancies, is well known. In such patients, histological abnormalities in the muscles have been described (Adams, Denny-Brown and Pearson, 1962). Hildebrand and Cöers (1967) incriminated cachexia to explain the histopathological abnormalities in their cancer patients with weight loss and emaciation. Tomlinson, Walton and Rebeiz (1964), on the other hand, reported histopathological abnormalities of varying degree in the majority of cachectic patients suffering from a variety of disorders including malignant disease. In contrast to these histopathological reports, cachexia *per se* has not been shown to produce any electrophysiological abnormalities. Buchthal (1970), in his patients with anorexia nervosa, and Campbell and McComas (unpublished, *see* Campbell and Paty, 1974), in their cachectic schizophrenics, did not find any electrophysiological abnormalities. Others have drawn similar conclusions (Croft and Wilkinson, 1963; Croft *et al.*, 1967; Trojaborg *et al.*, 1969).

SUMMARY

The present study deals with 195 patients with malignancies at various sites. These patients were evaluated clinically for any neurological dysfunction and, with 50 controls, were subjected to electrophysiological studies. The mean ages of patients and controls were $44{\cdot}93 \pm 10{\cdot}7$ years and $40{\cdot}98 \pm 14{\cdot}07$ years respectively ($P > 0{\cdot}05$).

Involvement of the central nervous system was found in 4 per cent. Muscle wasting was observed in 22 per cent and in half, this was associated with neuropathic symptoms. Generalized (14 per cent) wasting was more frequent and striking than proximal (7 per cent).

Electrophysiological studies revealed that generalized wasting was predominantly neuropathic. On the other hand, proximal wasting was 'myopathic', 'neuropathic', or 'neuromyopathic'. The electrophysiological studies unmasked latent abnormalities in 35 per cent of the clinically normal patients.

Various electrophysiological abnormalities were more common in malignancies of the lung, ovary, testes, penis, stomach, and oral cavity. Electromyographic and nerve conduction abnormalities were found in 32 per cent and 26 per cent respectively. The denervation pattern was the most common and the incidence of sensory, motor and sensorimotor neuropathy was 11 per cent, 8 per cent and 7 per cent respectively.

ACKNOWLEDGEMENT

The authors are greatly indebted to Professor T. P. Srivastava for his suggestions in preparing the manuscript and to Professor K. N. Udapa for his encouragement. Request for reprints to B.C.K.

REFERENCES

ADAMS, R. D., DENNY-BROWN, D. and PEARSON, C. M. (1962) *Diseases of Muscle. A Study in Pathology.* 2nd Edition, New York: Hoeber, p. 584.

BRAIN, W. R. and HENSON, R. A. (1958) Neurological syndromes associated with carcinoma. *Lancet*, ii, 971–975.

BUCHTHAL, F. (1970) Electrophysiological abnormalities in metabolic myopathies and neuropathies. *Acta Neurologica Scandinavica*, **46**, Suppl. 43, 129–176.

CAMPBELL, M. J. and PATY, D. W. (1974) Carcinomatous neuromyopathy. 1. Electrophysiological study. An electrophysiological and immunological study of patients with carcinoma of lung. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 131–141.

COHEN, H. L and BRUMLIK, J. (1968) *A Manual of Electromyography.* New York, Evanston and London: Hoeber Medical Division; Harper and Row, pp. 39–62.

CROFT, P. B., URICH, H. and WILKINSON, M. (1967) Peripheral neuropathy of sensorimotor type associated with malignant disease. *Brain*, **90**, 31–66.

—— and WILKINSON, M. (1963) Carcinomatous neuromyopathy. Its incidence in patients with carcinoma of the lung and carcinoma of the breast. *Lancet*, i, 184–188.

DOWNIE, A W. (1969) Studies in nerve conduction. In: *Disorders of Voluntary Muscles.* 2nd Edition. Edited by J. N. Walton. London: Churchill, pp. 789–795.

HILDEBRAND, J. and CÖERS, C. (1967) The neuromuscular function in patients with malignant tumours. Electromyographic and histological study. *Brain*, **90**, 67–82.

McLeod, J. G. (1975) Carcinomatous neuropathy. In: *Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas and E. H. Lambert. Vol. II. Philadelphia: W. B. Saunders, pp. 1301–1313.

Moody, J. F. (1965) Electrophysiological investigation into neurological complication of carcinoma. *Brain*, **88**, 1023–1036.

Shy, G. M. and Silverstein, I. (1965) A study of the effects upon the motor unit by remote malignancy. *Brain*, **88**, 515–529.

Skaria, J., Kattyar, B. C., Srivastava, T. P. and Dube, B. (1975) Myopathy and neuropathy associated with osteomalacia. *Acta Neurologica Scandinavica*, **51**, 37–58.

Thage, O., Trojaborg, W. and Buchthal, F. (1963) Electromyographic finding in polyneuropathy. *Neurology, Minneapolis*, **13**, 273–278.

Tomlinson, B. E., Walton, J. N. and Rebeiz, J. J. (1969) The effects of aging and of cachexia upon skeletal muscle—a histopathological study. *Journal of the Neurological Sciences*, **9**, 321–346.

Trojaborg, W., Frantzen, E. and Andersen, J. (1969) Peripheral neuropathy and myopathy associated with carcinoma of the lung. *Brain*, **92**, 71–82.

(*Received February 17, 1977*)

Brain (1978), **101**, 65-81

A STUDY OF THE VISUAL DEFECT IN VERBAL ALEXIA-SIMULTANAGNOSIA

by DAVID N. LEVINE *and* RONALD CALVANIO

(*From the Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA*)

INTRODUCTION

PATIENTS with posterior cerebral lesions often identify single visual items considerably better than compound items consisting of several components (Heilbronner, 1905; Pick, 1923; Wolpert, 1924; Pötzl, 1928; Kinsbourne and Warrington, 1962, 1963). In reading, the deficit is manifest as 'verbal alexia'. The patient has little difficulty identifying single letters of the alphabet, but has great difficulty reading words. He may name an incorrect word with the same first few letters as the word shown or may attempt to name the letters of the word sequentially with varying success in ultimately saying the correct word. In interpreting thematic pictures, the behaviour described initially as 'simultanagnosia' (Wolpert, 1924) appears. The patient may name many of the component items but fails to relate the situation or event depicted.

Several explanations of such behaviour have been proposed. Early workers (Wolpert, 1924; Pötzl, 1928) postulated a visual agnosia. They assumed that experience with compound visual arrays results in the development of procedures for perceiving the compound arrays as unities and that such procedures can be selectively lost. These procedures are specific for particular categories of visual material—hence reading and picture interpretation might be affected independently. Later investigators have emphasized the existence of a perceptual disturbance affecting all categories of visual material, but there has been no consensus on the nature of this disturbance. Ranschburg and Schill (1932), elaborating the hypothesis of Balint (1909), postulated a decrease in the quantity of 'attentional energy' available to perceive forms. The perception of only one or two forms exhausts the available energy, limiting the number of forms that can be perceived simultaneously. Luria (1959) and Luria, Praudina-Vinarskaya and Yarbus (1963) adopted a somewhat similar explanation, but emphasized that the weakened 'visual analyser' actively inhibits the perception of elements other than the one perceived. Perception of a complex array is thus faulty because perception adheres to the item perceived. Kinsbourne and Warrington (1962, 1963) undertook the only detailed experimental study of such patients. Using brief tachistoscopic presentations they found that the patients required no longer exposures to identify single items than did normal subjects. But unlike normals, the patients were unable to identify more than one item even with prolonged exposures. They postulated that in the normal, 'simultaneous perception' of multiple elements occurs sequentially, item by item. In the patients, the perceptual acts occur normally but the interval between such acts is inordinately prolonged. Finally, Bay (1953) has proposed that subtle deficits in the visual fields, detectable only with methods such as flicker perimetry or tachistoscopic sensation time, might produce an effective 'tunnel vision' that results in simultanagnosia when combined with a global dementia.

We have undertaken an experimental study of three patients with verbal alexia (simultanagnosia—disorders of simultaneous perception). We have studied visual perception by employing flicker perimetry to assess peripheral visual fields and tachistoscopic exposure thresholds for single letters to assess central vision. To detect subtle alterations in central vision, we have explored the effects of after-coming masking patterns on the perception of single letters. All these tests failed to disclose abnormalities that could explain the impairment in identification of compound stimuli. In exploring the latter, we found that the patients were quite successful in reporting pre-designated portions of a compound array but were not successful when the portion to be reported was designated by the examiner *after* exposure of the array. We found that errors made by our patients in identifying letters in a compound array were predominantly 'visual' in that the reported letter was morphologically similar to the stimulus letter. We confirmed this tendency toward 'visual' errors in an experiment requiring patients to state only whether three letters were identical or not. Finally, we have demonstrated that our patients retain the enhancement in perceptual span which is seen in normal subjects for letter sequences forming words compared to random sequences of letters. We conclude that the abnormality in these patients can be explained neither by an elementary perceptual deficit (in the sense of Bay) nor by an agnosia (in the sense of Wolpert). Both the concepts of impaired perceptual analysis and impaired visual short-term memory, however, adequately account for many of the patients' deficits. Impaired perceptual analysis appears to be the more satisfactory explanation, though difficulties arise even with this hypothesis.

Before presenting the experiments, we describe the clinical histories of the three patients. The clinical and laboratory data provide further evidence that the lesions resulting in verbal alexia (simultanagnosia, disorders of simultaneous perception) are localized in the left temporo-occipital region.

CASE REPORTS

C.C. (*MGH 190 92 60*), a 70-year-old, right-handed, retired bank treasurer developed the sudden inability to read on May 5, 1976. He complained of headache in the left parietal region. Letters 'seemed to run together'. In the past, he had been well except for the gradual onset of tremor in the left hand two years previously at which time a diagnosis of Parkinson's disease was made. The tremor gradually worsened, and one year before admission he underwent right stereotaxic thalamotomy with striking relief. When admitted on June 8, 1976, his major complaints were that he couldn't read, often could not think of the word he wished to say, and that his driving was poor.

On admission examination, he was alert and slightly hypokinetic. He was orientated to person, place, and time. Speech was fluently articulated, but conversation was marked by occasional pauses that suggested searching for the appropriate word. He usually selected the correct word from a dictated list when he could not say it spontaneously. He readily obeyed three-step commands involving touching of body parts, discrimination of right and left on his body, and discrimination among his fingers. Mental calculations were somewhat slow but were accurate. He repeated spoken language easily. Forward digit span was six. He spelled dictated words and named words spelled aloud accurately. His vocabulary was that of an educated man. He demonstrated good recent memory by showing the position of multiple objects hidden in his room after several minutes, by recognizing the examiner each time he met him, and by giving a consistent and fairly complete history as his dysnomic disability improved. He seemed to find his way about the hospital but showed considerable difficulty in a laboratory route-learning task.

He read very slowly, apparently not seeing more than one word and sometimes only part of a word in a single fixation. He required 125 seconds to read a 62-word fourth grade paragraph (Gray Oral No. 4). The beginning of this and other paragraphs was read more quickly than the middle or end. Mistakes almost invariably involved the right side of the word. Thus, 'they' was read as 'there', 'one' as 'once', 'there were' as 'therefore'. He would often get stuck at certain words such as 'them', 'garden', 'sunk'. He lost his place only occasionally when shifting to the beginning of a new line of print. He named singly-presented letters correctly. In interpreting a thematic picture, he usually named individual items accurately and tended to proceed from the left side of the picture to the right. But he was unable to get the sense of the pictures even when he had named the crucial component parts. He had marked difficulty naming colours, though he matched identical shades well and did well on the Ishihara colour plates. He could not name photos of famous people, though he indicated recognition by stating that he recognized the face, by describing the social function or position of the person in the photo, and by selecting the correct name from a dictated list.

He wrote spontaneous sentences and to dictation, quite legibly, with good orthography, except that writing was slightly cramped and messy, at least partially a result of his residual tremor. He copied the Rey-Osterrieth diagram slavishly and incompletely. The components represented were not malorientated.

Pupils were equal and reacted to light. Central visual acuity was 2/3 normal at 2 ft viewing distance in each eye. On confrontation testing, there was a delay in the detection of moving objects in the homonymous right fields, but not a complete hemianopia. Kinetic perimetry (Goldmann—4 mm^2 and 1 mm^2 targets) showed considerable but not a complete shrinkage of the right hemifields of each eye. Very slight shrinkage compared to the norms for age was present in the homonymous left fields. Flicker perimetry yielded normal values for age in the homonymous left fields and values 30 to 50 per cent of normal in the homonymous right fields. The range of eye movements was normal. The eyes were conjugate at rest. Tracking movements were good except for slight difficulty following targets into the right (amblyopic) field. Saccades appeared normal. Convergence to approaching objects was poor.

The remaining cranial nerves were normal. There was no limb weakness and only slightly increased tone in both elbows with mild cogwheel phenomenon. Stance was normal. There was slight scuffing and circumduction of the left leg as he walked. Reflexes were of normal amplitude except slightly more brisk on the right. Detection of pin-prick, light touch, vibration, and passive joint movement was normal in both hands and feet.

Technetium brain scan demonstrated a focal area of increased uptake in the left occipital region. Computerized axial tomography demonstrated a low absorption abnormality in the left occipital lobe extending to infero-medial temporal lobe. Arteriography demonstrated occlusion of the circummesencephalic portion of the left posterior cerebral artery with some reconstituting collaterals from distal branches of the left middle cerebral artery. EEG showed shifting posterior bi-temporal slowing.

R.T. (*MGH 069 70 92*), a 77-year-old, right-handed composer and professor of music, previously in excellent health, was conducting an orchestra on June 20, 1976, when he suddenly developed the sensation of being struck on the head. The following morning he seemed unable to find his way from the bathroom to the bedroom and needed assistance in packing his clothes. He seemed confused, was slightly unsteady, and had difficulty expressing himself. He was admitted that day to the Massachusetts General Hospital.

On examination, he was alert. He had marked difficulty finding the correct words in conversation. His responses were thus quite delayed, his phrases were often of decreased length, and he appeared frustrated with his inability to utter the correct word. His articulation was normal except for a tendency to stutter on the first syllable when trying to come up with a word. He repeated single words and short phrases accurately but showed verbal paraphasias with longer phrases. On the day of admission, he was unable to perform one-step verbal commands, though he often repeated them clearly but puzzlingly as though trying to ascertain their meaning. By the third day in hospital, he followed all one-step, several two-step, but no three-step commands. He was unable to name singly-presented printed letters or words, but by the end of the first week, he could write his name and a sentence to dictation, albeit with poor penmanship and an occasional doubling or omission of a letter. Copying print was nearly impossible. He had marked difficulty naming singly-presented colours and faces of well-known people, though he always indicated recognition of the latter by either describing the person's social position or selecting his name from a dictated list. He was slow, but more accurate in naming common objects. There was no apraxia of face, trunk or limbs. A right homonymous hemianopia was present. Optic discs were normal. Range of eye movements was full. There was slight right facial weakness. Strength in the limbs was normal. No defects in somatic sensation were present. Reflexes were slightly exaggerated on the right and a right-sided Babinski sign was present.

Lumbar puncture demonstrated yellow-pink CSF with 2500 RBCs/mm^3. X-rays of the skull were normal. Computerized axial tomography showed an area of increased density, consistent with hæmatoma in the left occipito-temporal region. EEG showed shifting and generalized slowing, more abundant and of lower amplitude on the left.

By the fourth week, speech reception had improved to the point that he obeyed most three-step dictated commands. He repeated four nonsense syllables accurately. Forward digit span was 5. Difficulty finding words in conversation persisted but had improved. He was slow and occasionally inaccurate in performing dictated mental calculations. He had only minor trouble demonstrating on his hand a named finger and had no trouble designating right or left of paired organs on his own body.

He was able to re-state fully a short, three-sentence dictated story after an interval of seven minutes filled with other verbal testing. His vocabulary was that of a highly educated man. He retained a quick and highly sophisticated sense of humour, and his social manners were impeccable, In interpreting proverbs, he began with a concrete simile but always arrived at a highly abstract interpretation.

He now named most single printed letters accurately (19/20, calling M, 'V') and named all colours (7/8) except one correctly, calling bright red, 'orange'.

He was unable to read. When given a first grade text (Gray Oral paragraph No. 1) to read, he performed as follows:

A boy had a dog	A--can--wa--was a---a dog!
The dog ran into the woods	The bog ran---uhdog ran into a---
	(What letters do you see?) w,a,a,d---a
The boy ran after the dog	The bog---b, o, g, ?ran onto the dog
He wanted the dog to go home	The---wander ran into---into---uh to---

The total elapsed time to this point was 150 seconds.

In other texts, he often resorted to spelling words letter by letter, often misnaming several of them. Contrastingly, he spelled aloud dictated words such as GHOST, LOVELY, and SURROUND and named words such as 'HANDLE', 'ENOUGH', and 'SAMPLE' spelled aloud by the examiner. He said about his reading, 'the words don't have a meaning' and 'I can't tell at one glance what a word is'.

When he was shown a picture depicting an event or situation, he named individual components of the picture accurately, but could not describe the situation or event. His writing continued to improve and was easily legible when he wrote spontaneous sentences or sentences to dictation. Copying handwriting was very difficult. He copied the complex Rey-Osterrieth diagram nearly accurately, but extremely slavishly, requiring a full twenty-five minutes to complete the copy.

Visual acuity with glasses was 1/5 normal, at 2 ft viewing distance. Kinetic perimetry confirmed a right homonymous hemianopia with moderate shrinkage of the intact visual field compared to age-matched controls. Flicker perimetry showed nearly normal flicker fusion frequencies in the intact left visual fields.

After the fourth week, he showed little change. Though returning weekly to the laboratory for testing (in which he participated eagerly) he never learned which door to take when leaving. In his own home, he was often unable to find the groceries or the cutlery drawer, stating that he could not remember where these items were located. Despite these disabilities, he always gave the impression of a highly intelligent and witty man, eager to improve and to get back to work.

G.C. (*MGH 209 10 10*), a 59-year-old, right-handed, machinist was in good health until July 23, 1976, when, while pulling a weed from his garden, he felt a sudden sharp pain 'as if someone had hit me on the head'. The pain lasted only thirty seconds and he remained asymptomatic until the following morning when he awoke with occipital headache. On examination at a local hospital, a homonymous right superior quadrantanopia was detected. He was referred to the Massachusetts General Hospital.

On admission, he was alert and orientated to person, place and time. His speech was fluent without paraphasia. He obeyed three-step verbal commands. He repeated spoken language normally. There was no difficulty with word finding in conversation. He named written words, common objects, colours, and faces of famous people accurately. He read fluently and grasped the situations depicted in complex pictures. Calculations were accurate. He showed no disturbance in demonstrating named fingers or right and left on his own body. He copied the complex Rey-Osterreith figure normally. Memory for short narrative stories was probably within normal limits.

A homonymous right superior quadrantanopsia was present. Optic fundi were normal. Visual acuity was 2/3 normal at 2 ft viewing distance in each eye. Range of eye movement was normal. Facial sensation and movement were intact. There was no limb weakness. Reflexes were symmetric. No Babinski signs were present. Somatic sensation was intact.

Skull x-rays were normal. Arteriography demonstrated an arteriovenous malformation deep in the left temporo-occipital region. It was fed by branches of the left posterior cerebral artery and drained into the vein of Galen. Computerized axial tomography showed an area of increased absorption medial to the occipital horn in the deep medial-occipital region. The mass, consistent with hæmatoma, extended to the surface of the occipital horn but was extrinsic to it. Three weeks later a second scan indicated that the hæmatoma had resolved.

In the fourth week in hospital, he underwent a left occipital craniotomy for microsurgical removal of the arteriovenous malformation. A cortisectomy was made, the centre of which was 6 cm above the transverse sinus and 2½ cm left of the midline. The incision was parasaggital of length 4 cm. At a depth of 2½ cm, a cyst with yellowish-brown fluid was encountered and partially removed. The ventricle was entered at the superolateral portion of the cyst. The feeding vessels were electrocoagulated, cut, and removed. After removal, persistent bleeding from the cortisectomy site required repeated efforts at hæmostasis and finally removal of a fresh hæmatoma. The cortisectomy was widened slightly laterally to remove a small amount of necrotic brain tissue. Total blood loss was less than one unit.

Immediately after operation, he awoke disorientated to place and time with a right homonymous hemianopia and with inability to name colours or single letters. By the third post-operative day, he was fully orientated, able to read single letters but often only the left-most portions of words. On detailed examination, two weeks after operation, he was alert and fully orientated. Speech was fluent without paraphasia or word-finding difficulty. He easily repeated spoken words and phrases and obeyed three-step dictated verbal commands. Auditory digit span was six forward. He was almost completely accurate in re-telling a three-sentence story after five minutes. Mental calculations were done well. He had no trouble demonstrating named fingers or right and left on his own body. He quickly named faces of famous people, single colours, and single letters.

When presented with a first grade text (Gray Oral Paragraph No. 1), he read slowly, word by word, requiring fifty-five seconds to read the 48 words. He misread 'dog' for 'boy', 'can't' for 'cannot', 'there' for 'then'. In another paragraph, the sentence 'The part of farming enjoyed most by a boy is the making of maple sugar' was read as 'The part . . . of family enjoyment . . . most be . . . must be a boy . . . in the making . . . of maps . . . maple sugar' and required thirty-five seconds. When given a thematic picture, he named individual items accurately but was unable to describe the situation or event depicted. He wrote intelligibly to dictation and spontaneously. He was very slow, but only slightly inaccurate in copying print. He gave up after completing approximately one-half of a copy of Rey-Osterrieth diagram in five minutes.

Visual acuity remained 20/30 and optic discs were normal. He had a dense, right homonymous hemianopia to confrontation. Kinetic perimetry confirmed the hemianopia and demonstrated moderate shrinkage of the intact left half of each visual field. Flicker perimetry demonstrated values approximately 2/3 normal in the homonymous left visual fields. Optic fundi were normal. The range of eye movements was full. Saccades appeared normal as he looked about the room. Following movements were normal except that he lost track of the object as it moved to the right (presumably a result of hemianopia). Optico-kinetic nystagmus was considerably less vigorous with the tape moving to the patient's left. Facial sensation and movement was intact.

There was no limb weakness. Reflexes were symmetrical. No Babinski signs were present. Somatic sensation was intact including naming of palpated objects in either hand.

A computerized axial tomographic scan, two days after operation, demonstrated a small left occipital hæmatoma at the site of operation. Arteriography, two weeks later, demonstrated disappearance of the arteriovenous malformation.

SPECIAL STUDIES

A three-field look-in tachistoscope (Gerbrands G1130), subtending 7° × 10° of visual angle, was used. Luminance in each field was 4 ft lamberts unless otherwise specified. The stimuli were one or more black capital letters (Chartpak-Helvetica 48 pt transfer letters) with a height of 1°, width of 0·6°–1·6°, and stroke width of 0·13° of visual angle on a white background (fig. 1).

In a given trial, the pre-exposure field was a 100 ms period of darkness and the post-exposure field was 200 ms of illuminated blank field (4 ft lamberts). At all times other than the pre-exposure, exposure, and post-exposure periods, the patient fixated a central fixation point against an illuminated (4 ft lamberts) background. The stimuli were always exposed to the left of the fixation point. When more than one letter was present, they were in a horizontal row unless otherwise specified. The distance from the fixation point to the left-most end of the left-most letter was never greater than 4° of visual angle. Trials were initiated by the experimenter after a verbal warning signal ('ready').

(1) *Impaired Identification of Multiple Visual Objects*

The first experiment measured the capacity to name single letters and to name multiple simultaneously-presented visual letters. First, a single letter (fig. 1, top left) was displayed at varying exposure times. For each exposure time, ten single letters were presented, and the minimum duration at which 9/10 were correctly named was noted. Patient R.T. could often draw single letters, though he was unable to name them, and in his case a correct drawing was accepted. Table 1 illustrates these threshold values for the three patients. The threshold values for three males of comparable age without neurological disease are also shown. Next, a set of consonant trigrams (fig. 1, top right) was displayed at varying exposure times. Twenty trigrams were presented at each exposure time, and the number of correctly named (or drawn) letters per trigram was tabulated as a function of exposure time for each patient (Table 2). It is evident

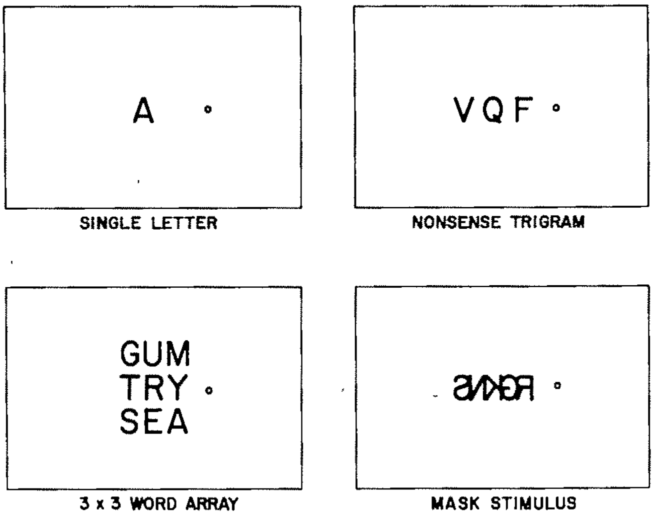


FIG. 1. Stimulus materials. The fixation circle is superimposed on stimulus materials in the figure to depict its approximate spatial relationship to stimulus contents.

TABLE 1. SINGLE LETTER THRESHOLD (MS)

Normal control group		*Patients*	
C.M.	13	C.C.	8
A.G.	10	R.T.	16
F.N.	6	G.C.	13

TABLE 2. LETTER CAPACITY* AS A FUNCTION OF EXPOSURE TIME

Patients	*Stimulus exposure time (ms)*					
	20	100	300	1000	2000	5000
C.C.	1·0	1·3	1·4	—	1·9	2·2
R.T.	0·8	1·4	1·2	1·3	—	1·4
G.C.	1·3	1·8	2·0	2·6	—	2·9
Control group	20	50				
C.M.	2·7	2·9				
A.G.	2·9	3·0				
F.N.	2·9	2·7				

* Letter capacity = average number of letters correctly reported from a trigram. Maximum score, three letters correctly reported.

that the number of letters reported correctly per trigram increased only very slowly with time. All three letters were not consistently reported even at exposure durations of several seconds. The control subjects, in contrast, were able to name all three letters almost always and achieved this ability at a duration of exposure at or just above the threshold duration for single tachistoscopically-presented letters.

(2) *Partial Report*

Although the patients were unable to report all the letters of the trigram in a single fixation, we wished to see whether they retained any flexibility in selecting by spatial position the letter or two that they were able to report. Accordingly, the patients were shown the same set of twenty trigrams used in the previous experiment, but before the exposure they were told to report only the 'left', the 'middle' or the 'right' letter. Each trigram was shown three times (on trials n, n+20, n+40) so that each letter of each trigram was cued once. The cued position varied pseudo-randomly from trial to trial. The results are shown in Table 3. It is evident that performance in this experiment was far superior to that of the previous experiment at all exposure durations.

TABLE 3. LETTER CAPACITY AS A FUNCTION OF EXPERIMENTAL CONDITIONS AND EXPOSURE TIME

	Exposure Time (ms)								
	20			100			300		
	Condition			*Condition*			*Condition*		
Patient	*Full*	*Pre*	*Post*	*Full*	*Pre*	*Post*	*Full*	*Pre*	*Post*
C.C.	1·0	1·6	1·3	1·3	2·0	1·5	1·4	2·3	1·8
R.T.	0·8	2·1	1·0	1·4	2·3	1·4	1·2	2·7	1·3
G.C.	1·3	2·6	—	1·8	2·7	1·7	2·0	2·7	2·0

Full = full report experiment. Pre = pre-stimulus cuing experiment. Post = post-stimulus cuing experiment.

A closer analysis of the data revealed that all patients performed nearly perfectly when asked for the left-most or the right-most letter but had varying degrees of difficulty reporting the middle letter. The same results were obtained when visual position cues were given instead of the verbal cues 'left', 'middle', and 'right'. (A horizontal bar appeared in a position just above the letter to be named before the trigram was exposed and remained visible during exposure of the trigram. Again only the middle letter of the array presented difficulty).

The patients were not nearly as successful when the cued position was given after the stimulus exposure instead of before. We performed an experiment identical in every detail with the experiment above except that we gave the cues 'left', 'middle', and 'right' one second after the offset of the trigram. The results are shown in Table 3. It is evident that performance was far poorer than in the pre-stimulus cuing experiment and about equal to the performance in Experiment 1 where all three letters had to be named.

(3) *Backward Pattern Masking*

Although the patients required no longer exposures to identify single letters than did normal subjects, we wished to explore the possibility of a more subtle impairment in the identification of single letters. To this end we compared the effects of aftercoming nonsense patterns in impairing identification of a single letter in our patients and in normal control subjects.

A single letter was exposed at a luminance of 0·5 ft lamberts for a duration just sufficient for it to be correctly named every time if followed only by darkness. Then, this duration having been determined, the effects of an aftercoming masking pattern of the same intensity as the target letter were studied. The mask, consisting of several partially superimposed letters (fig. 1, bottom right) completely covered the area of the initial letter. In a given experiment, the exposure duration of the mask and the interval between offset of the initial stimulus and onset of the mask (inter-stimulus interval) were systematically varied. First, a mask exposure duration was selected. The inter-stimulus interval was gradually increased from 0 ms every time a wrong answer was given until the patient was able to name the initial letter (presented at the threshold duration) on three successive trials. The inter-stimulus interval above which masking did not occur (the 'critical inter-stimulus interval'—ISI) was measured. The data are presented in Table 4. It is clear that there is little difference between the critical inter-stimulus intervals in patients and controls.

TABLE 4. CRITICAL INTER-STIMULUS INTERVAL (MS) AS A FUNCTION OF MASK DURATION

		Mask Duration				
Patient	*SL thresh.*	*T*	*2T*	*4T*	*8T*	*Median*
C.C.	T=25	120	80	100	100	100
R.T.	T=30	120	100	—	200	120
G.C.	T=25	40	100	60	40	50
Control	*SL thresh.*	*T*	*2T*	*4T*	*8T*	*Median*
L.B.	T= 7	40	80	100	100	90
F.N.	T=40	10	80	80	50	65

SL thresh = single letter threshold. Mask duration is measured in integral multiples of single letter threshold, (T).

(4) *Matching*

Thus far, the patients had been required to identify (by naming or drawing) the stimulus elements. We wished to determine whether the deficit would be manifest where the patient was required to attend to all the elements in the compound array, but where identification was not required. In this experiment, nonsense trigrams were presented in all of which at least two of the three letters were identical. The third letter was either (1) identical to the other two, (2) different from the other two in a striking way morphologically (for example, KCK or XOX), (3) different from the other two in a morphologically more subtle way (for example, XKX or COC). The position of the odd letter in the trigrams of Conditions 2 and 3 varied pseudorandomly in a balanced fashion over trials. On a given trial, the patient was required to state 'same' if all the letters of the trigram were identical, and 'different' if one of the letters was different from the other two. An equal number of trigrams with identical and non-identical components were shown. The results are shown in Table 5.

It is clear that performance in this experiment was superior to that in Experiment 1 when measured in terms of the percentage of trials on which a correct response was given. However, even though the trigrams were presented for durations greatly exceeding the threshold for the naming of individual letters, errors were not rare. These consisted both of calling trigrams with identical letters 'different' and trigrams with an odd letter 'same'. Of note, the latter type of error occurred only when the different letter resembled the other two morphologically.

TABLE 5. PERCENTAGE OF CORRECT MATCHING RESPONSES AS A FUNCTION OF STIMULUS TYPE

Patient	*Exposure time (ms)*	*Same*	*Stimulus type different (MS)*	*Different (MD)*
C.C.	50	83	63	100
R.T.	50	76	81	100
G.C.	20	88	79	100

Same = all elements identical (e.g. 000). Different (MS) = one element different, but morphologically similar (e.g. OCO). Different (MD) = one element different, and morphologically distinctive (e.g. OOX).

(5) *Analysis of Errors*

In the course of Experiments 1 and 2, it appeared that the errors in letter identification were by no means random. To confirm this impression, we undertook an analysis of over 1500 errors, approximately 500 consecutive errors per patient. An error of identification was recorded when the patient could neither name nor draw the simulus letter. Of these, the majority, approximately 80 per cent, were omissions; the subject stated that he did not know or was unable to 'see' the letter in question; 5 per cent of the errors were simple transpositions; the subject named a correct letter but in the wrong position—for example, saying 'S' when asked to name the middle letter of the trigram NWS. The remaining errors are shown in Table 6. It is evident that only a very limited set of letter names were uttered for each letter stimulus. Of the errors committed three or more times (O for Q, W for V, O for C, W for N, V for W, W for K, G for C, Q for C, C for G, H for R, Q for G, C for Q) all are clearly morphologic errors, that is, the letter reported resembles the stimulus letter in shape.

TABLE 6. ERRONEOUS RESPONSES

Letter presented	*Erroneous response and its frequency*	*Letter presented*	*Erroneous response and its frequency*
B	T(2), K(2)	N	W(6), M, H, I
C	O(8), G(5), Q(4), D	P	F, D, T, B
D	O(2), P, Q, G	Q	O(22), C(3), D(2), G(2), B
F	E(2), P(2), T, L, W	R	H(3), N(2), B, P, S
G	C(3), Q(3), B(2), O, D, S	S	X, B, L
H	I, W	T	I(2), N
J	L, C, W	V	W(9), Y(2), L
K	W(5), R, F	W	V(5), M
L	I(2), T	X	S(2), L, Z
M	W(2), N(2)	Z	V

(6) *The Reporting of Words vs Non-words*

In a final experiment, we attempted to test directly the hypothesis that loss of strategies for perceiving compound arrays acquired through experience lies at the source of verbal alexia - simultanagnosia. To this end we compared the patients' ability to identify letters in commonly encountered sequences, such as words, to their ability to identify nonsense consonant trigrams.

In the first part of the experiment, the patients were shown a set of mixed trigrams, half of which were common three-letter English words and half of which were nonsense trigrams. They were told only 'We are going to show you, each time, three letters that we have picked at random from the alphabet. Name (or draw) every letter you see'. The first two trials consisted of nonsense trigrams to reinforce the expectation that words would not be present. Stimuli were presented for 100 ms—five to ten times threshold for single letters (*see* Table 1). The number of correct letters reported was compared for the word and non-word stimuli. The results are shown in columns one and two of Table 7. In the second part of this experiment, the words and non-words were separated from each other and presented in two separate blocks. Before the block of words was presented, the subject was told that he would be shown a three-letter word each time and to try to name the letters of the word. Before the block of non-words, he was told that he would be shown three letters that did not form a word and that he should try to name the letters. The number of correct letters reported was again compared for words and non-words. The results are shown in columns three and four of Table 7.

TABLE 7. LETTER CAPACITY AS A FUNCTION OF EXPECTANCY AND STIMULUS STRUCTURE

	Expect non-words		*Expect words*	*Expect non-words*
Patient	*Words*	*Non-words*	*Words*	*Non-words*
C.C.	1·5	1·1	3·0	1·1
R.T.	2·1	1·3	2·1	1·2
G.C.	1·8	2·0	2·9	2·4

Stimulus duration 100 ms.

In all patients, the letter capacity was greater for words than for non-words in the blocked condition. In the unblocked condition, where every attempt was made to drive the subjects' expectations toward non-words and so to minimize guessing (i.e., inference as to a letter's identity without perception of the letter), the letter capacity remained greater for words than for non-words in patient R.T. and in C.C., but showed no difference in G.C.

Once it was recognized that the patients were indeed capable of naming three-letter words, even at durations of exposure where only one or two letters of nonsense trigrams could be reported, we attempted to measure the capacity for three-letter words as a function of exposure time. The stimulus card for each trial contained three common, three-letter English words written one above the other (fig. 1, bottom left). Twenty such stimulus cards were used at each exposure time. Every attempt was made to encourage the patient to treat the words as units. He was told in advance that he would be shown three-letter words and was encouraged to name the word rather than component letters. The results are shown in Table 8.

TABLE 8. WORD AND LETTER CAPACITY AS A FUNCTION OF EXPOSURE TIME

	Exposure time			
	100 ms		*300 ms*	
Patient	*Letter capacity*	*Word capacity*	*Letter capacity*	*Word capacity*
C.C.	1·3	0·6	1·4	0·8
G.C.	1·8	0·8	2·0	1·3

Word capacity = average number of words correctly reported from a display containing three three-letter words (*see* fig. 1, *bottom left*). Maximum score = three words correctly reported. Letter capacity taken from Table 1. Maximum score: three letters correctly reported.

It is clear that capacity for three-letter words increases slightly with exposure time just as does the capacity for letters. The capacity for three-letter words is approximately one-half that for individual letters.

The results of this experiment indicate that patients retain the ability to expand their visual letter span when the letters form words.

DISCUSSION

The three patients presented here clearly correspond to those previously described under the terms 'simultanagnosia' (Wolpert, 1924), 'verbal alexia' (Pötzl, 1928; Misch and Frankl, 1929; Ranschburg and Schill, 1932), and 'disorders of simultaneous perception' (Kinsbourne and Warrington, 1962). Clinically, in addition to right homonymous hemianopia or hemiamblyopia, the patients displayed inability to report the event or situation depicted by a multicomponent picture though they named individual items serially and usually accurately. They were unable to read most words at a glance and could report only one or two letters in a single visual fixation. Anatomically, all three patients had unilateral left-sided lesions in the inferior temporo-occipital region.

The results of our experiments argue against an explanation of the disability in terms of a narrow 'effective' visual field in the sense of Bay (1953). Flicker fusion frequencies in the left homonymous visual fields were nearly normal in all patients as were the fields tested with routine kinetic perimetry. Nor can a subtle defect in macular or paramacular visual perception be invoked. Tachistoscopic sensation time for single letters was normal or nearly normal in each patient, and aftercoming masking patterns did not interfere with the identification of letters any more than in control subjects. Our results thus confirm the conclusions of those investigators (Wolpert, 1924; Kinsbourne and Warrington, 1962) who argued that the abnormality underlying the syndrome of verbal alexia - simultanagnosia is not one of central visual acuity or of peripheral visual fields.

We also tested directly the hypothesis that loss of acquired procedures for efficient perception of commonly experienced arrays is the basis of verbal alexia-simultanagnosia (Wolpert, 1924). The patients all identified more letters when these formed a word than when they were random consonants. These results are inconsistent with Wolpert's hypothesis. They complement the data of Kinsbourne and Warrington (1962), demonstrating that the deficit in simultaneous form identification is not limited to any specific category of visual material and the data of Warrington and Rabin (1971), showing that patients with left posterior cerebral lesions improve their performances in tasks of visual letter identification when the letter sequences more closely approximate those of written English. Thus, a material specific visual 'simultanagnosia' in the sense of Wolpert is not present.

Having established that the deficit can be explained at neither the most elementary level of visual perception, nor in terms of a supraperceptual 'gnostic' function, we are left with three hypotheses postulating deficits at intermediate levels of perception and memory: (1) a prolonged refractory period between otherwise normal acts of visual letter perception (Kinsbourne and Warrington, 1962); (2) impaired capacity for discrimination of visual features of stimulus arrays (Balint, 1909; Ranschburg and Schill, 1932; Luria, 1959; Luria *et al.*, 1963); (3) impaired visual short term memory (Warrington and Rabin, 1971).

The theory of the prolonged refractory period is based on the assumption that normal perception of compound arrays consists of sequential 'all or none' perceptions of single elements separated by a refractory period. In verbal alexia-simultanagnosia the 'all or none' acts occur normally but are separated by a prolonged refractory period. If this were so, the number of letters identified by patients should increase linearly with exposure time, but at a slope smaller than that of normals. With sufficient exposure time, the number of letters identified should be normal. Such was not the case with our patients (Experiment 1). Also, since the perceptual acts are 'all or none' and do not interfere with one another, the errors should be random rather than morphological in nature. This again was not the case in our patients (Experiments 4 and 5). We do not know why Kinsbourne and Warrington (1962) failed to observe the non-randomness of errors that we observed and which had been reported by others (Pötzl, 1928; Ranschburg and Schill, 1932). Perhaps the co-occurrence of other systematic errors, such as transpositions and perseverations lent a pseudo-randomness to the errors which could be clarified only by the realization that *multiple specific* determinants of errors existed.

The theory of insufficient capacity for feature discrimination can account for most of our experimental results. The identification of one or two elements of an array exhausts the patients' limited capacity. Nevertheless, they retain considerable flexibility in deciding which of the letters of an array to analyse with their limited capacity (Experiment 2). If they attempt to divide their perceptual capacity among a larger number of letters while maintaining the depth of discrimination required to identify these letters, they make errors because the perceptual capacity per letter is less than required for the task. The errors reflect morphological similarity to the actual target because they are the products of some, though too shallow, discrimination (Experiments 4, 5). Thus, discrimination may have proceeded to sufficient depth to discriminate X from C but not O from C. When only a single form need be identified, however, the time course of perception is normal (Experiments 1, 3) because the now undivided perceptual capacity is sufficient for the task of identification. If the task is made easier by requiring only a determination of whether three letters differ or are the same (that is, if the required depth of discrimination is decreased) the perceptual span may enlarge. Thus, the patients perform better in the matching task than in a task requiring identification, and within the matching task the incidence of errors is directly related to the required depth of discrimination (Experiment 4). Finally, if the task is eased not by changing the judgment required, that is, the task remains one of letter identification, but by changing the stimuli to highly familiar letter sequences, the span again enlarges.

Thus, as in normal subjects (Miller, Bruner, and Postman, 1954; Bruner, 1957) our patients perform better with three-letter words than with nonsense trigrams (Experiment 6).

Ultimately, however, the theory of insufficient feature discrimination capacity is too broad in scope. All our patients had no difficulty identifying faces, whereas we have observed several patients with difficulty identifying faces but no verbal alexia. The latter patients, in agreement with reports of many other investigators (Pallis, 1955; Bornstein and Kidron, 1959; Beyn and Knyazeva, 1962; Lhermitte, Chain, Escourolle, Ducaine and Pillon, 1972; Lhermitte and Pillon, 1975), are impaired not only in identifying faces, but in identifying items belonging to other categories whose members differ only subtly from one another along multiple dimensions—that is, where a high degree of discrimination is required. Examples include identification of landscapes, buildings, animals, and models of automobiles. Thus, tasks requiring identification of a single, though complex, visual pattern appear to have a different neuropsychological basis from tasks requiring the identification of a *compound* array consisting of multiple identifiable components, where misidentification of any component will usually impair identification of the array. A comprehensive theory of deficits in visual identification must explain this double dissociation; the theory of insufficient visual feature analysis outlined here does not.

The hypothesis of impaired visual short-term memory (STM) can also account for the experimental results. In attributing the deficient visual span in our patients to STM, however, one must modify the concept of STM to an extent that makes this hypothesis indistinguishable from the feature analysis hypothesis just discussed. Warrington and Shallice (1969) introduced impaired STM into the neurological literature by interpreting the defect in repeating spoken language in their patient K.F. in terms of impaired auditory STM. K.F.'s visual span exceeded his auditory span; and the authors argued for independent neuropathological substrates for impaired auditory and visual spans. Warrington and Rabin (1971) found that patients with left posterior cerebral lesions were impaired in visual span and that correlation between visual and auditory spans was low. We confirm the independence of impaired visual and impaired auditory spans by presenting patients with severe, selective deficits in visual span only. Auditory digit spans in all patients were normal.

It is thus tempting to interpret our experimental results in terms of defective visual STM, just as Warrington and Shallice interpreted the results of repetition aphasics like K.F. in terms of defective auditory STM. Indeed, the parallels in experimental results are striking. Pre-stimulus cuing with auditory strings improves performance in repetition aphasics (Kinsbourne, 1972) just as it does in our patients with visual strings (Experiment 3). Post-stimulus cuing in contrast does not improve performance either in repetition aphasics with auditory strings (Warrington and Shallice, 1969; Kinsbourne, 1972; Strub and Gardner, 1974) or in our patients with visual strings. Matching of auditory strings is done better than repetition of the strings, but is still not normal (Warrington and Shallice, 1969; Kinsbourne, 1972; Strub and Gardner, 1974). The same is true for visual matching in our patients. Finally, the capacity for repetition increases with slower rate of dictation of the string (Warrington and Shallice, 1969; Strub and Gardner, 1974) just as longer tachistoscopic exposure time improves the capacity of our patients to identify a visually presented string.

A closer analysis of the nature of the deficit in visual span in our patients, however, demonstrates the lack of adequate differentiation between perception and short-term memory as the latter must be conceived to account for the experimental results. The normal course of backward pattern masking in our patients demonstrates that the impairment is not in the 'iconic store' (Sperling, 1960; Neisser, 1967) that provides the raw material for perceptual analysis. Since auditory short-term memory is also normal, the deficit must be at a stage between the iconic store and auditory STM, perhaps the 'visual recognition buffer' postulated by Sperling (1967) in his three component (icon→visual recognition buffer→auditory STM) model. This view of verbal alexia-simultanagnosia was expressed by Warrington and Rabin (1971). However, to conceive of the deficit as one of STM as opposed to perceptual analysis one must be able to distinguish the two operationally. One must, for example, show that information in the visual buffer arrived normally (that is, perceptual analysis was intact) but either decayed abnormally rapidly or was subject to some form of inter-element interference. It is precisely this that we have been unable to show. Indeed the opposite seems to be the case. When no 'memory load' in terms of elapsed time between stimulus offset and report was imposed, the patients were still impaired. This condition occurred in Experiment 1 where patients were unable to identify more than two letters even with exposure times of five seconds (and in informal trials for exposures of over a minute) in which report was completed while the letter array was still exposed. This suggests that information in the visual buffer is never normal. In other words, perceptual analysis—the read-out of information from iconic storage into the visual recognition buffer—is impaired.

SUMMARY

Three patients with lesions of the left occipito-temporal lobes and the clinical picture of verbal alexia-simultanagnosia are presented. In tachistoscopic experiments, the patients identified single letters at very short, normal exposure durations. Aftercoming 'masking' patterns did not impair their ability to name single letters more than for normal subjects. When presented with three letters simultaneously, the patients would name only one or two even with very long exposures. If told in advance which letter to name they successfully reported any single letter of the trigram except for varying difficulty with the middle letter. If told only after the exposure which letter to name, they performed poorly. If they were required to state only whether the three letters were identical, performance was better than

for naming. Errors occurred when the odd letter resembled the other two morphologically. The naming of letters of a trigram was better when the letters formed a word than when they did not. Errors consisted of morphological confusions and transpositions of other elements of the trigram. These experimental results can be interpreted as a deficit in the perceptual analysis of compound visual arrays.

ACKNOWLEDGEMENT

We thank Drs. Robert Crowell, Ernest Picard and Robert Young for the opportunity to study their patients. We also thank Dr. Ernst Wolfe who performed the tests of flicker and kinetic perimetry. We are grateful to Drs. Raymond Adams, C. M. Fisher, Norman Geschwind, James Lackner and J. P. Mohr for reviewing the manuscript and offering helpful suggestions. This research was supported in part by grants to D.N.L. from the National Institute of Neurologic Disease and Stroke (1 R01 NS 13102-01) and from the Rowland Foundation.

REFERENCES

BALINT, R. (1909) Seelenlähmung des 'Schauens', optische Ataxie, räumliche Störung der Aufmerksamkeit. *Monatschrift für Psychiatrie und Neurologie*, **25**, 57-71.

BAY, E. (1953) Disturbances of visual perception and their examination. *Brain*, **76**, 515-550.

BEYN, E. S. and KNYAZEVA, G. R. (1962) The problem of prosopagnosia. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 154-158.

BORNSTEIN, B. and KIDRON, D. P. (1959) Prosopagnosia. *Journal of Neurology, Neurosurgery and Psychiatry*, **22**, 124-131.

BRUNER, J. S. (1957) On perceptual readiness. *Psychological Review*, **64**, 123-152.

HEILBRONNER, K. (1905) Studien über eine eklamptische Psychose. *Monatschrift für Psychiatrie und Neurologie*, **17**, 277-381, 425-460.

KINSBOURNE, M. (1972) Behavioral analysis of the repetition deficit in conduction aphasia. *Neurology, Minneapolis*, **22**, 1126-1132.

—— and WARRINGTON, E. K. (1962) A disorder of simultaneous form perception. *Brain*, **85**, 461-486.

—— —— (1963) The localizing significance of limited simultaneous visual form perception. *Brain*, **86**, 697-702.

LHERMITTE, F., CHAIN, F., ESCOUROLLE, R., DUCAINE, B. and PILLON, B. (1972) Étude anatomoclinque d'un cas de prosopagnosie. *Revue Neurologique*, **126**, 329-346.

—— and PILLON, B. (1975) La prosopagnosie. Role de l'hemisphère droit dans la perception visuelle. *Revue Neurologique*, **131**, 791-812.

LURIA, A. R. (1959) Disorders of 'simultaneous perception' in a case of bilateral occipito-parietal brain injury. *Brain*, **82**, 437-449.

—— PRAUDINA-VINARSKAYA, E N. and YARBUS, A. L. (1963) Disorders of ocular movement in a case of simultanagnosia. *Brain*, **86**, 219-228.

MILLER, G. A., BRUNER, J. S. and POSTMAN, L. (1954) Familiarity of letter sequences and tachistoscopic identification. *Journal of General Psychology*, **50**, 129-139.

MISCH, W. and FRANKL, K. (1929) Beitrag zur Alexielehre. *Monatschrift für Psychiatrie und Neurologie*, **71**, 1-47.

NEISSER, U. (1967) *Cognitive Psychology*. New York: Appleton-Century-Crofts, Chapter 2.

PALLIS, C. (1955) Impaired identification of faces and places with agnosia for colors. *Journal of Neurology, Neurosurgery, and Psychiatry*, **18**, 218-224.

PICK, A. (1923) Zur Zerlegung der 'Demenz'. *Monatschrift für Psychiatrie und Neurologie*, **54**, 3-10.

PÖTZL, O. (1928) Die Aphasielehre vom Standpunkte der Klinischen Psychiatrie. In: *Handbuch der Psychiatrie*. Leipzig und Wien: Franz Deuticke.

RANSCHBURG, P. and SCHILL, E. (1932) Über Alexie and Agnosie. *Zeitschrift für die Gesamte Neurologie und Psychiatrie*, **139**, 192-240.

SPERLING, G. (1960) The information available in brief visual presentations. *Psychological Monographs*, 74, No. 11.

—— (1967) Successive approximations to a model for short-term memory. *Acta Psychologica*, **27**, 285-292.

STRUB, R. L. and GARDNER, H. (1974) The repetition defect in conduction aphasia: mnestic or linguistic? *Brain and Language*, **1**, 241-255.

WARRINGTON, E. K. and RABIN, P. (1971) Visual span of apprehension in patients with unilateral cerebral lesions. *Quarterly Journal of Experimental Psychology*, **23**, 423-431.

—— and SHALLICE, T. (1969) The selective impairment of auditory verbal short-term memory. *Brain*, **92**, 885-896.

WOLPERT, I. (1924) Die Simultanagnosie-Storung der Gesamtauffassung. *Zeitschrift für die Gesamte Neurologie und Psychiatrie*, **93**, 397-415.

(*Received March 16, 1977*)

Brain (1978), **101**, 83-117

MENTAL PHENOMENA EVOKED BY ELECTRICAL STIMULATION OF THE HUMAN HIPPOCAMPAL FORMATION AND AMYGDALA

by ERIC HALGREN, RICHARD D. WALTER, DIANA G. CHERLOW *and* PAUL H. CRANDALL

(*From the Brain Research Institute, Reed Neurological Research Center, and Department of Surgery/ Neurological, UCLA School of Medicine, Los Angeles, California 90024*)

INTRODUCTION

ELECTRICAL stimulation of the human brain may evoke reports by patients of a wide variety of simple and complex sensations, emotions, and cognitions. These mental phenomena have been primarily considered in relation to the localization of function within the human brain. When a relatively simple sensory sensation is evoked, interpretation in this context appears to be straightforward. Consider, for example, the observation that electrical stimulation of a striate cortex locus very reliably results in a sensation corresponding in modality and spatial location to the sensation evoked by natural stimulation of the anatomically related retinal locus (Brindley and Lewin, 1968). In this case, it seems reasonable to presume that the specific sensations during which a cortical locus will be activated by natural stimuli are predicted by the characteristics of the sensations evoked by electrical activation of that same point. A similar interpretation may be applied to the discrete and topographically organized somæsthetic sensations evoked by stimulation of the post-central gyrus (Libet, Albers, Wright, Delattre, Levin and Feinstein, 1964).

Penfield, in his pioneering studies describing the mental phenomena evoked by stimulation of the human temporal lobe, interpreted these evoked phenomena in a manner analogous to those evoked by specific sensory cortex stimulation. Penfield found, and others have confirmed, that the most common categories of mental phenomena evoked by temporal lobe stimulation include complex hallucinations (Baldwin, 1960; Horowitz, Adams and Rutkin, 1968; Penfield and Perot, 1963; Sem-Jacobsen and Torkildsen, 1960), feelings of familiarity (*déjà vu*) (Mullan and Penfield, 1959), alimentary sensations (Jasper and Rasmussen, 1958; Kim, 1971; Van Buren, 1961), fear or anxiety (Chapman, 1960; Heath, 1964), and amnesia (Bickford, Mulder, Dodge, Svien and Rome, 1958; Brazier, 1966;

Chapman, Walter, Markham, Rand and Crandall, 1967; Pampiglione and Falconer, 1960; Serafetinides, Walter and Cherlow, 1975). When discussing the hallucinations, which he considered to be memories, Penfield labelled the temporal cortex 'memory records' (Penfield and Jasper, 1954, p. 145). When considering the *déjà vu* or other misinterpretations of present sensations, Penfield (1958) referred to this cortex as 'perceptual' in analogy to 'visual' or 'motor' cortex, because stimulation there evoked 'psychical responses' corresponding to the visual sensations or movements evoked by stimulation of the specific cortices.

As more experience has been obtained with the mental effects of temporal lobe stimulation, it has become clear that there are several properties of these effects that distinguish them from the behavioural consequences of specific sensory cortex stimulation. Mental responses to temporal lobe stimulation show a marked variability between different patients, and between different stimulations of the same patient (Pampiglione and Falconer, 1960; Van Buren, 1961). A certain category of mental phenomena may be evoked in only a minority of patients (for example, hallucinations: Penfield and Perot, 1963; Van Buren, 1961) and any one patient may only experience a minority of the possible categories. Pampiglione and Falconer (1960) and Van Buren (1961) have commented on the difficulty of obtaining a similar experience upon repeated stimulation of the same electrode, although Ervin, Mark and Stevens (1969) seem to suggest greater reliability. Many stimulations, even among those that evoke after-discharges, fail to evoke any mental phenomena (Angeleri, Ferro-Milone and Parigi, 1964; Chapman, 1958; Pampiglione and Falconer, 1960; Walker and Marshall, 1961).

What is responsible for this diversity and variability of mental response? Valenstein (1973) summarizes strong evidence from stimulation of various animal brain sites (particularly the rat hypothalamus) that the pre-existing temperament of the animal stimulated may be a better predictor of which behaviour is obtained than the precise location of the stimulating electrode. Other authors have offered clinical observations of a limited number of stimulations of the human medial temporal lobe that support a similar conclusion. For example, Kim and Umbach (1973) have commented that amygdala stimulation only yields aggressive behaviour in 'aggressive patients'. Heath, John and Fontana (1968) report that intense pleasure is only derived from medial temporal lobe or 'septal' stimulation in patients with pre-existing intense physical or psychic pain. Fear occurred upon stimulation in Van Buren's (1961) series only in those patients whom he felt were apprehensive regarding the stimulating session *per se*.

The relative contributions of precise electrode location, in comparison with personality factors, in defining the mental phenomena evoked by temporal lobe stimulation has been most widely investigated with respect to the content of complex hallucinations. It has been possible to interpret certain evoked auditory (Mahl, Rothenberg, Delgado and Hamlin, 1964), gustatory-olfactory (Rayport and Ferguson, 1974), and visual (Ferguson, Rayport, Gardner, Kass, Weiner and Reiser, 1969) hallucinations as symbolically related to ongoing psychodynamic processes, as inferred from supplementary psychiatric interviews and dream reports, and from analysis of the interpersonal situation in which stimulation occurred. In contrast, the localizationist interpretation, proposed by Penfield (1958), and Penfield and Jasper (1954), is that the hallucinations, no matter how bizarre, are in fact memory images, and that which particular memory is evoked is a matter of which engram happens to be closest to the stimulating electrode. This interpretation seems unlikely. First, hallucinations are usually associated with after-discharges (Horowitz, Adams and Rutkin, 1968; Ishibashi, Hori, Endo, and Sato, 1964), and after-discharges imply widespread electrographic effects. Second, stimulation of widely separated anatomical areas may evoke similar hallucinations (Horowitz *et al.*, 1968; Penfield and Perot, 1963). Third, repetition of stimulation with the same electrode, location, and stimulus parameters, produces, according to most authors, different images (Baldwin, 1960; Weingarten, Cherlow and Halgren, 1976; Horowitz *et al.*, 1968). Lastly, excision of the area where the stimulating electrode was placed does not eliminate the memory of the experience which was evoked by stimulation there (Baldwin, 1960).

These challenges to the localizationist interpretation have been countered by the proposal that certain engrams could be highly localized but yet could be evoked by distant stimulation if the engram is activated or sensitized by an epileptic process (Bickford *et al.*, 1958; Penfield and Perot, 1963). Penfield and Perot (1963) supported this proposal with their observation that stimulation of the temporal lobe was only able to evoke hallucinations from temporal lobe epileptics, and not in patients with foci in other lobes. However, as Penfield and Jasper (1954) noted, the temporal lobes of patients with non-temporal foci were not stimulated as extensively as those of patients with temporal foci. Since only about 8 per cent of the temporal lobe epileptics whom Penfield stimulated did experience hallucinations of formed images (Penfield and Perot, 1963), this evidence must be considered inconclusive. In any case, a critical role of the epileptic pathology in selecting which patients experience hallucinations, and which hallucinations they experience, is clearly contradicted by the reports of Ishibashi *et al.* (1964) and Sem-Jacobsen (1968) that stimulation of the surface and depths of the temporal lobes of non-epileptic schizophrenics may result in formed visual hallucinations.

The above discussion regarding the factors selecting the mental phenomena evoked by temporal lobe stimulation is based on observations that, while very valuable, are isolated and qualitative. In as much as the anatomical site, stimulus parameters, and patient all tended to vary from stimulation to stimulation it was not possible to rigorously isolate the particular factor responsible for the mental effects. In this paper, the anatomical sites sampled were held relatively constant across patients by adherence to a constant set of stereotaxic co-ordinates. The use of chronically implanted electrodes permitted the complete exploration of the capacity of all implanted sites to evoke mental phenomena when stimulated according to a regular protocol of stimulus parameters. This, and the noting of the amperage, frequency, and electrographic effects of each stimulation, established the comparability of stimulus characteristics across patients. Of course, the patient-related characteristics, such as aura, personality and location of focus, all remained constant across the average of 100 stimulus trains applied to each patient. Thus, the effects of patient-related variables could also be separated from the effects of electrode site and stimulus parameters. This study represents a first attempt at evaluating the factors selecting the mental responses to temporal lobe stimulation. The results indicate that a mental phenomenon was seldom evoked until the strength of stimulus was sufficient to induce widespread evoked potentials and after-discharges. The type of experience then reported was related to patient-specific variables including, specifically, their personality, rather than to the precise locus of the stimulating electrodes.

METHODS

The subjects were 36 psychomotor epileptics participating in a comprehensive programme for the study and treatment of partial epilepsy (Clinical Neurophysiology Program: CNP). The average age was 26±8 years (range 10–44); 13 were female; 3 were left-handed. The patients were given thorough neurological, psychological, and surface electroencephalographic examinations. If, after repeated attempts at control with medications, the patient's seizures continued to constitute a severe socio-economic handicap, then implantation of depth electrodes was considered in order to localize the seizure focus and thus direct surgical treatment (Crandall, Walter and Rand, 1963; Walter, 1973). Depth electrodes were not recommended for patients considered unlikely to tolerate electrodes or to benefit from seizure reduction due to their physical condition (for instance, repeated serious infections or progressive CNS disease) or mental status (for instance, severe mental retardation or psychosis). The procedures reported here followed the guidelines for the protection of human subjects in clinical research promulgated by the National Institutes of Health, U.S. Public Health Service in 1971 and 1974. The research protocol was approved by the UCLA Human Subjects Review Committee. Patients were fully informed of the steps in the research procedures both during interviews and in explicit written form.

Of the 36 patients described here, an operable temporal lobe focus was identified in 28 (21 right; 7 left) during the approximate four-week course of depth and surface EEG studies (for criteria, *see* Walter, 1973). Of the 27 that elected an anterior temporal lobectomy (for results, *see* Crandall, 1975), adequate histology reports were available from 22. Pathology consisted of hippocampal sclerosis (13 patients), hamartoma (2 patients), gliosis (2 patients), or an astrocytoma III (one patient). No pathology was found in 4 patients. Brown (1973) and the Scheibels (1973) have provided more detailed descriptions of the pathology observed in the CNP series. Information regarding specific patients in the above papers may be correlated with the results presented here by reference to the CNP patient numbers.

Electrode implantation sites were, bilaterally, the amygdala (AM), and the anterior (A), middle (M), and posterior (P), hippocampus (HC) and hippocampal gyrus (HCG). In addition, bilateral electrodes were placed in 5 patients into the uncus (Un), and in 2 patients into the anterior (AN) and centre median (CM) nuclei of the thalamus. In a further 2 patients electrodes were placed into the CM but not AN. In Patient 49, electrodes were also implanted in the cingulate gyrus and orbital cortex. This paper is concerned with the experiential effects of stimulating the mesial temporal structures. The effects of stimulating the other regions, however, will be referred to for purposes of comparison.

Stereotaxic placement of depth electrodes followed the technique of Talairach, David and Tournoux (1958), as it has been modified by one of us (P.H.C.). Filling of the ventricles with contrast medium (Conray) permitted the direct visualization of the hippocampus and amygdala where they indent the temporal horns of the ventricles. The image of the temporal horn defined the stereotaxic axis of reference from which electrode co-ordinates were calculated for the temporal sites (Talairach *et al.*, 1958) and thalamic sites (Talairach, David, Tournoux, Corredor, and Kvasina, 1957). Self-tapping hollow stainless steel screw-guides were placed in the skull according to these co-ordinates. Epoxylite insulated stainless steel electrodes were then inserted through the screw-guides to the calculated depth and locked in place. Only electrodes whose co-ordinates were confirmed by x-ray at this point to be within the limits specified for the intended structure were included in the present study. The electrodes were either coaxial, with a 0·20 mm diameter wire inside a 0·55 mm tube and a tip separation of 1 mm, or bi-polar, with 0·25 mm wires and a tip separation of 1·5 mm. The exposed electrode surface at either pole was approximately 0·009 cm^2, resulting in a transfer resistance ranging from 4·7 to 12·5 Kohms, with a mean of about 7 Kohms. All 7 electrodes and screw guides protruding from each temporal bone were connected together into a rigid structure with Kadon dental cement. The scalp was then covered with a sterile head dressing from which passed only the electrode leads.

The over-all accuracy of this stereotaxic technique was evaluated by one of us (P.H.C.) in lobectomy specimens from 13 unselected patients of the CNP series. Of the 69 depth electrodes which had been placed in these temporal lobes, 62 (90 per cent) terminated, according to operative radiographs, within the intended anatomical locus. Histological examination of serial sections of the resected lobes revealed small condensed clusters of astrocytes where the stimulating electrodes had been located. The site where the electrode had terminated, indicated by a characteristically denser gliotic aggregation, was found for 51 of the 69 placements. In general, electrode tips which could not be localized lay beyond the posterior and medial margins of the resection. For example, the resections were never carried out sufficiently posterior to include the posterior hippocampal placement within the surgical specimen

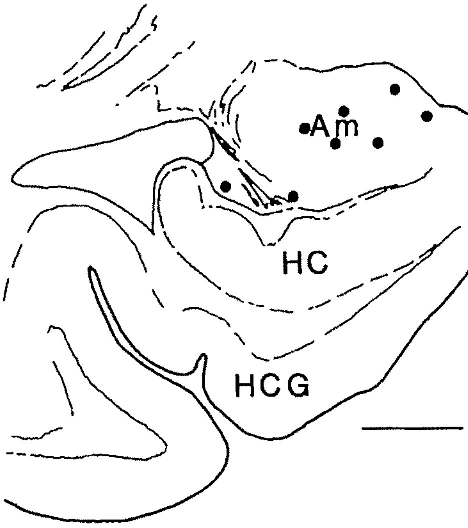


FIG. 1. The actual sites of termination of 8 electrodes stereotaxically directed toward the amygdala are plotted against a tracing of a normal frontal section. Bar = 5 mm.

As is shown in fig. 1, all amygdala electrodes terminated within the lateral, basal, or accessory basal nucleus (the basolateral complex); the medial rotation (Humphrey, 1972) and relatively small size of the corticomedial amygdala complex in humans (Crosby and Humphrey, 1941) renders it unlikely that we stimulated that structure. Most hippocampal gyrus electrodes (fig. 2) terminated within the entorhinal cortex (area 28 and possibly area 34 of Brodmann, 1909) although errant electrodes could also possibly terminate in the presubiculum (area 27), perirhinal cortex (area 35), or neocortex (area 35; equivalent

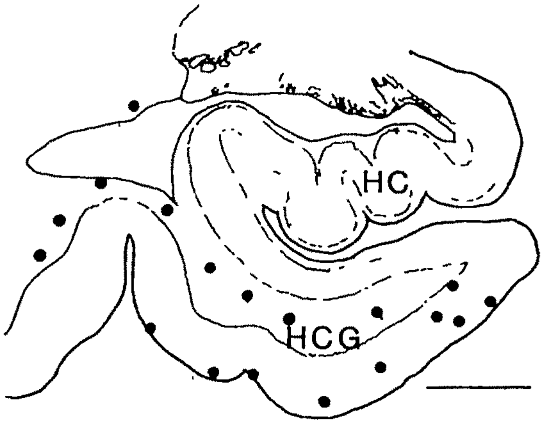


FIG. 2. The terminations of 18 electrodes directed toward all levels of the hippocampal gyrus are plotted against a frontal section of a normal anterior hippocampal gyrus. Bar = 5 mm.

to area TH of von Economo, 1927). Hippocampal electrodes (fig. 3) terminated in all fields of Ammon's horn, and in the dentate gyrus. The over-all accuracy of the stereotaxic technique was 88 per cent: 45 of the 51 histologically identified electrode terminations were within the intended zone. It should be noted that in no case was histological confirmation available for electrodes stereotaxically directed to structures outside the medial temporal lobe.

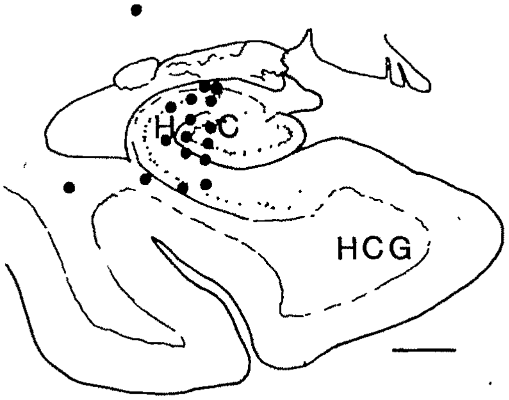


FIG 3. The terminations of 17 electrodes directed toward the anterior, middle or posterior hippocampus are plotted against a frontal section at the level of the middle hippocampus. Bar = 5 mm.

The electrical stimulation session(s) was generally conducted two to three weeks after implantation. Initially, the purpose of the stimulation session was to evoke a clinical aura or seizure and thus provide information regarding which side initiated the patient's seizures. Later, improvements in telemetred recording methods permitted the side of origin to be determined directly from spontaneous seizures. At this point, the stimulations were continued with the purpose of determining the intactness of memory functions in the side contralateral to the origin of the spontaneous seizures. It was reasoned that if memory functioned adequately during an after-discharge in the diseased temporal lobe, then it would also remain functional if that lobe were removed surgically.

The stimulation sessions for each patient lasted several hours, often on two or more days. The order of electrodes stimulated varied from patient to patient. An electrode was stimulated with a Grass S-8 stimulator using the Lilly wave-form, with balanced 100 microsecond pulses of opposite polarity separated by a 300 microsecond interval. The first stimulation of a given electrode was with a low frequency and voltage (usually 5 volts at one pulse per second). These stimuli were usually presented in twenty-second trains. However, the trains would be terminated earlier if widespread strong evoked responses were observed. Successive stimulus trains were of successively higher frequency and voltage. The highest frequency stimuli which were applied to a given electrode could vary from one to 30 pulses per second, but was usually 10 pps. The maximum current passing through the electrode, as monitored across a parallel load, was limited to 10·0 mA (current CNP practice limits current level to 5·0 mA). Stimulation of a given electrode was terminated when this current was attained, or when a clinical seizure or long after-discharge was produced. Another electrode site was then stimulated in the same manner. There was generally at least thirty seconds between stimulation trains applied to the same site and two minutes between stimulation trains applied to different sites. Following an after-discharge or clinical seizure, no stimulation was applied until the EEG returned to baseline. An array of 15 electrodes plus stimulus marker were monitored on a Grass Model 78 Polygraph. Usually the monitored electrodes lay in the mesial temporal structures, but, occasionally cortical activity was monitored through stainless steel orthopædic nails insulated except for 2 mm of the tip and placed in the outer table of the skull according to a modified 10–20 international EEG system.

During the stimulation session, the patient was alone, lying on a bed in a small, sound-attenuated room. In the adjacent room was a neurologist (R.D.W.) applying the stimulation, an observer noting the parameters and effects of each stimulus train, and two technicians. The patient and the neurologist communicated by microphones and earphones. The neurologist's microphone was turned off when he was not talking to the patient. Thus, the patient was aware of neither the period, location, parameters, nor electrographic effect of the stimulus. During most stimulus trains, we depended upon the patient's spontaneous report to indicate that a mental phenomenon had been elicited. However, if an after-discharge occurred, the patient's orientation and memory of recent events was actively probed by a series of questions (for example, 'What did you have for breakfast?', 'What is the name of your doctor and hospital?', 'What is today's date, your birthdate?'). The later patients were also monitored by a closed circuit television system.

The neurologist's and patient's voices were recorded on tape. From a verbatim transcription of this tape, and the observer's notes, a protocol was made, listing for each stimulus train the parameters of stimulation, the location of evoked potentials and after-discharges, and any feelings or sensations reported by the patient. The electrographic responses noted during the stimulation were checked at a later date by reference to the paper record of the EEG. From the protocol thus obtained the characteristics of the stimulus trains evoking each category of mental phenomena were tabulated.

RESULTS

Description of Mental Phenomena

Highly diverse mental phenomena were reported. These phenomena were classified into 20 categories. Unless otherwise specified, the descriptions below refer to phenomena reported during stimulation of mesial temporal structures.

(*1*). *Visceral* (*heart*), *Ht* (3 patients, 3 electrodes, 5 stimulations): patient feels his heart beating faster (3,3,3) or harder (1,2,2).

(*2*). *Visceral* (*alimentary*), *Al* (16,32,59): patient reports a sensation in the alimentary tract. This was the most commonly reported experiential response. All except two of these reports referred to a region including the stomach. These reports (1,1,2) were of constrictions of the throat. Most commonly, the sensation was described as nausea (5,10,17). The next most common report described a sensation rising from the stomach to the throat (4,5,6). Related to this were simultaneous sensations of the throat and stomach (3,5,6) and sensations of being 'about to belch' (1,4,11). The remaining reports described constricted or 'sucked in' (2,4,4), dropping (1,2,2), cold (1,2,2), or unspecified (7,8,8) sensations referred to the stomach. In addition to the above responses, stimulation in the region of one patient's left anterior thalamic nucleus repeatedly resulted in a 'hollow' sensation in the stomach (1,1,6).

(*3*). *Motor*, *Mo* (9,11,14): patient reports a movement of his body. Most commonly, this movement was a localized twitch (2,2,3) tremor (3,3,5) or small displacement (4,5,6). The patients perceived all the above movements as being induced by an agent outside themselves.

(*4*). *Somæsthetic* (*head*), *Hd* (8,14,17): sensations in the head described by the patient as pulsing (1,1,1), tingling (1,1,2), tickling (1,1,2), burning (1,1,1), hot (1,1,1), headache (3,3,3), light (1,1,2), odd (1,3,3), or funny (1,1,2). The quality of one sensation was unspecified. Stimulation in the presumed region of the centre median nucleus also induced feelings in the head (2,3,28) described as 'like pins and needles' (1,1,10), 'tingling' (1,2,6), or as a metallic taste in the mouth (1,1,12). Interestingly, stimulation of the patient who felt a 'tingling' in her face and mouth upon presumed stimulation of the right or left centre median, felt the same sensation when stimulation of the right anterior hippocampal gyrus evoked potentials in the presumed centre median, bilaterally.

(*5*). *Somæsthetic* (*chest*), *C* (10,12,13). sensation in the chest described by the patient as painful (1,1,1), bad (1,1,1), like falling (1,1,1), full (1,1,1), warm (1,1,1), cold (1,1,1), or strange (2,5,6). One patient who could not remember any aura associated with her seizure did report an aura-like sensation in her chest. A sensation 'like pins and needles' in the chest was also reported after stimulation of the centre median nucleus of the thalamus (1,2,8).

(*6*). *Somæsthetic* (*limbs*), *L* (6,13,17): sensations in the hands, arms, or legs, described by the patient as tingling (2,2,5), pulsing (1,1,1), numb (3,3,3), aching (1,1,1), constricting (1,1,1), loosening (1,1,1), funny (1,1,1), or odd (2,2,2). The qualities of two sensations were not specified. In addition to the above reports, stimulation of the presumed centre median led to contralateral sensations described as 'pins and needles' (1,2,16) or 'tingling' (1,2,2).

(*7*). *Somæsthetic* (*whole body*), *WB* (6.8.9): sensations, which seemed to be spread over most of the body, described by the patients as tingling (1,2,2), numbness (1,1,1), tense (1,1,1), strange (1,1,1), or odd (1,1,2). The quality of two sensations were unspecified. One stimulation of the presumed left centre median resulted in a sensation of pins and needles on the right side of the body.

(*8*). *Temperature*, *T* (8,11,15): patient feels a hot (5,8,8) or cold (3,3,7) sensation. Of these, four stimulations were associated with a sensation localized to a particular part of the body (eyes, head, shoulder, or back).

(*9*). *Spatial illusions*, *SI* (6,8,8): this included three types of responses: (i) an illusional translation of the entire body with respect to the environment (4,5,5); (ii) an illusional movement of the environment (1,1,1); and (iii) dizziness (2,2,2).

(*10*). *Déjà vu*, *DV* (5,11,19): patient either reported '*déjà vu*' (5,9,10) or an 'aura' (2,5,9) which was known to include *déjà vu*.

(*11*). *Unformed auditory hallucinations*, *Au* (6,12,17): patient experiences a sound she describes as clicking (1,1,1), buzzing (2,5,7), ringing (1,1,1), or popping (1,2,2). Stimulation of the left anterior hippocampus in one patient at 20 V, 1 PPS, 5·6 mA resulted in a sound like 'water dripping'. Increasing the parameters of stimulation to 30 V, 5 PPS, 9·2 mA resulted in auditory sensation of increased intensity (like a 'hammer and nail'). A further stimulation of the left anterior hippocampal gyrus that resulted in an after-discharge throughout the left depth was accompanied by 'awful weird sounds'. This is the only case we have observed which seemed to show a relation between intensity of stimulation and intensity of sensation. However, even in this case, sequential stimulation of the left anterior hippocampus at higher frequency and equal amperage did not result in any reported mental phenomenon.

(*12*). *Unformed visual hallucinations*, *V* (4,5,9): patient reports seeing flashing (1,2,3), fluttering (1,1,2), blinking (1,1,1), or undescribed (1,1,3) lights.

(*13*). *Dream-like hallucinations*, *D* (6,6,9): hallucinations of formed visual images were classified as dream-like if they were described by the patient as being like a dream (3,3,4), day dream (1,1,1), movie (1,1,1), television programme (1,1,2), or cartoon (1,1,1).

(*14*). *Memory-like hallucinations*, *Me* (6,21,35): the remaining formed hallucinations, of which all but one were stated to be memories by the patients (5,20,34), were classified as memory-like. Thirty-seven of the forty-four memory and dream-like hallucinations were reported by 3 of the 36 patients (CNP Nos. 16, 49, and 53). Case histories and descriptions of hallucinations have been presented elsewhere for Patients 16 (Chapman, Walter, Markham, Rand and Crandall, 1967) and 53 (Weingarten *et al.*, 1976). Patient 49's seizures began when she was 12 years old as a general rigidity. She was able to hear and perform certain movements, but she was unable to talk. Intense fear accompanied these attacks. As she grew older, her seizures assumed a stronger motor involvement. Usually her head would turn to the right, followed by loss of consciousness and right-sided jerking. These seizures were sometimes preceded by an aura of 'buzzing' and *déjà vu*. Repeated attempts at control with medications were unsuccessful. A complete neurological and psychiatric examination was performed. The patient was considered to have strong displaced fears and phobias, and to display anxiety and tension with ruminative, obsessional and shy behaviour. Depth electrodes implanted at the age of 32 years recorded interictal

EEG paroxysmal spikes arising most frequently in the right anterior hippocampus and right middle hippocampal gyrus. However, EEG spikes also arose independently in the left depth. A spontaneous clinical seizure displayed a generalized onset, precluding surgical treatment.

TABLE 1. RESPONSES OF PATIENT 49 TO STIMULATION

Site stimulated	*No. of trains in sequence*	*Maximum pulses/s*	*Maximum current*	*Potential evoked?*	*After-discharge?*	*Déjà vu?*	*Hallucination?*
LAm	8	10	6·4 mA	—	—	—	—
LAHC	8	10	9·0	✓	—	—	—
LMHC	7	10	10·0	✓	—	DV	—
LPHC	8	10	8·0	—	—	—	—
LAHCG	8	10	6·4	✓	—	—	M
LMHCG	9	10	8·6	✓	✓	—	D,D
LPHCG	8	10	6·8	✓	—	DV	—
LMHC	1	10	10·8	✓	—	—	—
RAm	9	10	9·0	✓	✓	—	M,M,M
RAHC	7	10	8·4	✓	—	—	—
RMHC	8	10	9·0	✓	—	—	M,M,M,M
RPHC	7	10	8·8	—	—	—	—
RAHCG	5	10	6·4	✓	✓	DV	M*
RMHCG	7	10	9·2	✓	—	—	M
RPHCG	7	10	7·8	✓	—	—	M*M*
RUn	5	1	9·4	✓	—	—	M*
LMHCG	1	10	8·0	✓	✓	—	D
RAHCG	1	10	3·4	✓	✓	—	M
			2 weeks later				
LAm	6	1	9·4	—	—	—	—
LAHC	10	10	8·0	✓	—	DV,DV,DV	—
LCG	8	10	7·4	—	—	—	—
RAm	6	10	10·4	✓	—	DV	—
RAHC	9	10	8·0	✓	✓	DV,DV	—
RMHCG	9	10	6·8	✓	✓	DV	—
RCG	7	10	6·0	—	—	—	—
LOC	6	5	6·6	—	—	—	—
RAHC	2	10	8·2	✓	✓	—	OH,U
LAN	6	5	8·8	—	—	—	—
LVA	5	5	7·2	—	—	—	—
ROC	5	5	4·4	—	—	—	—
RAN	5	5	5·8	—	—	—	—
RVA	5	5	5·0	—	—	—	—

Each row of this Table presents a sequence of stimulus trains applied to the same site. L = left; R = right; A = anterior; M = middle; P = posterior; Am = amygdala; HC = hippocampus, HCG = hippocampal gyrus; Un = uncus; CG = cingulate gyrus; OC = orbital cortex; AN = anterior thalamic nucleus; VA = ventral anterior thalamic nucleus. All mental phenomena indicated were obtained with the highest stimulation current used, or else were repeated with all higher current levels, unless marked by an asterisk. M—memory-like hallucination; D—dream-like hallucination

Memory-like or dream-like hallucinations were evoked by seventeen separate stimulus trains applied to any one of eight different electrodes located bilaterally in Patient 49's medial temporal lobe (Table 1). Three of her hallucinations seemed to her like television shows—a 'soap opera' and programmes regarding implants or astronauts. The astronaut programme seemed 'like a dream, a weird dream'. She spontaneously remarked that she did not remember having had the dream before. The remainder of her hallucinations she reported to be specific memories: a trip to Yosemite or to Reading; a scene in her home; lying on a couch watching football; a particular telephone conversation; a chocolate coke she drank once in a small town. Two of her memories were of seizures, one which had occurred in junior high school and another at her home. Events that presumably were of great personal importance were also remembered: her brother's graduation from college and her son's first day in school. The latter 'memory' was the only one that was repeated. Even in this instance it was not clear if the specific images were re-experienced, or if the memories were only related. In all other cases, repeated stimulus trains applied to the same site, evoking potentials in the same recorded areas, would evoke apparently unrelated memories.

In general, when stimulation did not evoke potentials in other structures, either because of the low current used or the insensitivity of the stimulated site, no *déjà vu* or hallucination was evoked. When high current levels evoked widespread responses, then usually either *déjà vu* or a hallucination occurred, although often no mental phenomenon was reported. For any sequence of stimulations of the same electrode, only one category of mental phenomena was reported, although that category may be repeated with several stimulus trains within that sequence (*see* Table 1). Late in the stimulation session of Patient 49, the above pattern broke down to some degree; in three sequences isolated memory-like hallucinations occurred at current levels which did not evoke potentials, and were not repeated at higher current levels which did.

Two weeks later, Patient 49 underwent a second stimulation session. In this session, in addition to deep temporal sites, bilateral recordings were made from the presumed regions of the cingulate gyrus and orbital cortex, and the anterior and ventral anterior thalamic nuclei. No memory- or dream-like hallucinations were reported in this session. However, *déjà vu* was repeatedly observed, often from electrodes which in the previous session had yielded, with the same stimulus parameters, hallucinations but not *déjà vu*. Stimulation of the thalamic and cortical sites evoked no reported response, either mental or electrographic. These leads, however, did record potentials when the deep temporal leads were stimulated. Specifically, all deep temporal sites stimulated, with the exception of the left amygdala, evoked potentials in the ipsilateral orbital cortex, usually at threshold currents equal to or below those necessary to evoke potentials in ipsilateral deep temporal lobe structures. In addition, anterior hippocampal stimulation evoked potentials in both thalamic sites.

Patients 16 and 53 exhibited a similar relation between stimulus trains and evoked mental phenomena as Patient 49; in general, mental phenomena belonging to only one category would be evoked by a given stimulus sequence applied to a single site, although a later sequence applied to the same site may yield a different category. Again, mental phenomena tended to occur only with high current levels that evoked widespread electrographic responses.

(*15*). *Other hallucinations, OH* (4,5,6): hallucinations that were not clearly an unformed sensory hallucination nor were unambiguously a complete image.

(*16*). *Emotion, E* (8,16,35): in all cases, the emotion was unpleasant: fear (5,12,29) tension (1,1,1), or nervousness (1,1,1). Only one patient (CNP No. 32) reported feelings of anger, and no patient displayed overt aggression, upon stimulation of the temporal lobe. Patient 32 was a 24-year-old right-handed woman. Her seizures began with feelings of anxiety and progressed to salivation and clonic jaw movements. She gave the clinical impression of a passive-dependent personality. The bilateral recordings included four right depth structures: amygdala, anterior and middle hippocampus, and middle hippocampal gyrus. Upon stimulation of the right middle hippocampus at 7·5 mA and 10 pps, the patient remarked that she 'felt bad'. When the current was increased to 9·2 mA the patient 'felt like crying'. The patient felt 'hard to get along with' and heard a 'clicking noise' when the same stimulus parameters were applied in the following train. Thirty stimulus trains later (several of which were accompanied by nausea), stimulation of the right amygdala (10 pps, 15 V, 3·6 mA) evoked a brief after-discharge in the ipsilateral anterior and middle hippocampus. The patient reported 'nausea' and then a feeling of 'anger' The following stimulus train (10 pps, 20 V, 5·0 mA) induced nausea and a report of hearing something in Spanish, but no after-discharge and no anger All the above stimulations of Patient 32 which evoked mental phenomena also evoked potentials in all recorded ipsilateral structures. However, the converse is not true—most stimulations which evoked potentials evoked no mental phenomenon.

(*17*). *Confusion, Cf* (11,17,18): difficulty in thinking, disorientation for time and place.

(*18*). *Amnesia, Ae* (7,9,10): usually, the amnesia seemed to be for the events of the past several hours, but in one case it appeared to be confined to the previous few minutes (1,1,1), and in other cases was accompanied by the disruption of remote memory implied by disorientation (4,4,4).

(*19*). *Seizure, Sz* (6,8,9): a clinical seizure.

(*20*). *Unclassified, U* (10,15,22): the patient's report (feeling 'vague', 'funny', 'eerie' or 'strange') was not sufficiently defined to classify the experience.

In several instances, a single stimulation evoked mental phenomena from more than one category. These instances are tabulated in Table 2.

Characteristics of Stimulations that Evoked Mental Phenomena

Of 3495 stimulations of the mesial temporal lobe, only 267 elicited a mental response. Mental phenomena were much more likely to occur in response to stimuli which also evoked detectable electrographic responses. As is shown in Table 3, only 2·4 per cent of those stimuli that evoked no electrographic response were associated with a mental response. In contrast, 5·5 per cent of the stimuli that evoked a potential but no after-discharge, and 36·2 per cent of the stimuli evoking an after-discharge also evoked mental phenomena. This association of electrographic and mental responses was highly significant ($\chi^2 = 480{\cdot}2$, df $= 2$,

TABLE 2. MORE THAN ONE MENTAL PHENOMENON REPORTED DURING A SINGLE STIMULUS TRAIN

	Ht	Al	Mo	Hd	C	L	WB	T	SI	DV	Au	V	D	Me	OH	E	Cf	Ae	Sz
Ht																			
Al	1																		
Mo																			
Hd		2																	
C		4																	
L	1	3			1														
WB		2		1															
T	1	4		2	2		1												
SI		1						1											
DV	2	3				2	1												
Au			1		1			1		6									
V											3								
D	1							1											
Me		3				1				1									
OH		3					2												
E	1	5		1				3	1		1		1	1	1				
Cf					1				1										
Ae	1	2			1	1		2		1			2			1	4		
Sz																1			

Ae = amnesia, Al = visceral (alimentary), Au = unformed auditory hallucinations, C = somæsthetic (chest), Cf = confusion, D = dream-like hallucinations, DV = *déjà vu*, E = emotion, Hd = somæsthetic (head), Ht = visceral (heart), L = somæsthetic (limbs), Me = memory-like hallucinations, Mo = motor, OH = other hallucinations, SI = spatial illusions, Sz = seizure, T = temperature, V = unformed visual hallucinations, WB = somæsthetic (whole body).

P, 2-tailed, $< 0{\cdot}001$). It should be noted, however, that a clear majority of even those stimuli that evoked after-discharges were *not* accompanied by a reported mental phenomenon.

Stimuli which evoked bilateral after-discharges were particularly effective in eliciting mental phenomena: 69 per cent of such stimulations evoked a mental phenomenon, most often (14/19) Cf, Ae, or Sz. However, only 4 out of the 36 stimuli that evoked bilateral evoked potentials were associated with a mental phenomenon, and in 3 of those 4, the phenomenon was not reported until the potentials developed into after-discharges. Furthermore, similar phenomena were reported by the same patients during stimuli that elicited no contralateral electrographic response. Thus, there were no patients in which the appearance of bilateral evoked potentials appeared either necessary or sufficient for a particular mental phenomenon to occur.

TABLE 3. PERCENTAGE OF STIMULATIONS EVOKING A MENTAL PHENOMENON: CATEGORIZATION BY SITE OF ELECTRODE AND BY ELECTROGRAPHIC RESPONSE

	Site							
		HC			*HCG*			
Electrographic response	*Am+Un*	*Anterior*	*Middle*	*Posterior*	*Anterior*	*Middle*	*Posterior*	*Total*
No ER or AD	2·5	2·3	3·4	2·8	0·9	2·0	2·5	2·4
n =	324	215	119	211	111	101	127	1179
ER, no AD	8·2	7·6	8·4	2·1	4·8	3·3	1·3	5·5
n =	354	344	250	141	272	337	224	1922
AD	41·3	44·6	27·0	42·0	44·8	29·7	6·5	36·2
n =	46	112	37	7	58	74	31	365
Total	7·3	12·1	8·6	3·3	9·1	6·8	2·1	7·6
n =	724	671	406	359	441	512	382	3495

ER = evoked response AD = after-discharge.

Table 3 also shows that the probability of evoking mental phenomena differed among anatomical sites ($\chi^2 = 47{\cdot}03$, df = 6, P, 2-tailed, $< 0{\cdot}001$). In particular, the stimulation of the posterior electrodes elicited mental phenomena only about one-quarter as often as did stimulation of anterior electrodes. This comparison is inflated somewhat by the fact that stimuli applied to posterior sites were also less likely to evoke an electrographic response; but, when only those stimuli that evoked an after-discharge are considered, the differential frequency of mental phenomena when stimulating different sites is maintained ($\chi^2 = 19{\cdot}49$; df = 6; P, 2-tailed, $< 0{\cdot}01$), as it is when those stimuli evoking an evoked potential, but no after-discharge, are considered separately ($\chi^2 = 25{\cdot}77$; df = 6; P, 2-tailed, $< 0{\cdot}001$) (the expected frequencies were too low to conduct the χ^2 test on those stimuli that evoked neither an evoked potential nor after-discharge). Thus, it appears that there is an influence of site upon the probability of evoking mental phenomena, independent of the site's electrographic excitability. However, this cannot be strictly concluded because of the grossness with which electrographic responses were classified; for example, the potentials evoked by stimulation of posterior sites may be more restricted spatially than those evoked more anteriorly.

Conversely, the high probability that stimuli which evoked after-discharges would also evoke mental phenomena, noted above, was also inflated by this tendency for after-discharges to occur more frequently in anterior sites. However, consideration of the relation between evoking mental responses and evoking electrographic responses from these sites individually again yielded probabilities less 0·001 in every site (except the posterior hippocampal gyrus, in which the expected cell frequencies were too small to apply the χ^2 test).

TABLE 4. CHARACTERISTICS OF STIMULATIONS THAT EVOKED EACH CATEGORY OF MENTAL PHENOMENA

	Repeated behaviour		*Related to aura?*					
Mental category	*Increased amperage*[1]	*Same parameters*[1]	*Stimulus trains*[1]	*Patients*[2]	*ER or AD*[1]	*AD*[1]	*Left/Right*[3]	*Diseased/ Non-diseased*[4]
Ht	2/3	0/1	0/5	0/3	5/5	4/5	0/4	5/0
Al	22/30	11/15	31/58	8/15	57/58	36/58	29/29	22/26
Mo	3/11	0/0	1/14	1/9	10/14	4/14	7/7	8/6
Hd	3/11	0/0	1/17	1/8	15/17	6/17	4/11	8/4
C	2/5	1/4	6/13	3/9	13/13	7/13	6/7	6/7
L	4/12	2/4	0/17	0/6	15/17	8/17	10/7	5/10
WB	2/3	1/3	0/9	0/6	8/9	6/9	2/4	3/3
T	4/7	2/2	0/15	0/8	15/15	9/15	10/4	4/11
SI	0/1	0/0	2/8	1/6	5/8	4/8	4/4	3/4
DV	3/7	8/10	18/19	4/5	19/19	12/19	4/5	4/4
Au	3/7	4/4	9/17	2/6	14/17	7/17	5/6	5/5
V	3/4	2/2	3/9	1/4	4/9	3/9	2/6	7/2
D	2/3	3/5	0/9	0/6	9/9	9/9	3/2	3/3
Me	10/17	6/8	1/35	1/6	32/35	10/35	14/7	6/14
OH	1/3	0/0	0/6	0/4	6/6	4/6	0/4	0/3
E	15/21	10/15	26/35	3/8	35/35	24/35	19/14	22/9
Cf	1/5	1/6	3/18	1/11	18/18	15/18	12/5	5/8
Ae	0/2	2/5	0/10	0/7	10/10	10/10	7/2	2/7
Sz	0/2	2/2	0/9	0/6	9/9	9/9	4/5	4/4
U	4/12	2/3	0/22	0/9	19/22	7/22	14/4	1/13
Total A (stimuli that evoked a mental phenomenon)	70/136	41/61	74/267	14/36	238/267	132/267	125/106	97/111
			Total B (all stimuli)		2287/3495	365/3495	1607/1583	1521/1254
			Chi-square[5]		71·8	471	1·74	6·07
			P, 2-tailed <		0·001	0·001	n.s.	0·05

[1] Numerator is the number of stimulus trains evoking the specified category of mental phenomena and possessing the indicated characteristic. The denominator indicates the number of trains which could have possessed this characteristic. [2] Of those patients who experienced the indicated mental phenomenon during stimulation, this is the proportion who had previously experienced a similar phenomenon as part of their spontaneous aura. [3] Only stimuli applied to right-handed patients were considered for this column. [4] A hemisphere was considered 'diseased' if it was the electrographic locus of onset of spontaneous clinical seizures, the contralateral hemisphere was labelled 'non-diseased'. Patients with generalized or bilateral independent seizure onset were not included in this column. [5] χ^2 was calculated for the 2×2 table of stimulus trains: characteristic$^+$ versus characteristic$^-$, and mental phenomenon$^+$ *vs* mental phenomenon$^-$, as calculated from Total A and Total B. For key to abbreviations *see* Table 2.

A tendency to evoke widespread potentials and/or after-discharges was characteristic of stimulations evoking mental phenomena in each category (Table 4). Among these, dream-like hallucinations and amnesia were notable in that these phenomena were always accompanied by an after-discharge. The variability of the mental response is emphasized by the observation that when the same electrode that evoked a particular mental phenomenon was stimulated again with the same parameters, in only 41 of 61 cases was a mental phenomenon of the same category obtained (Table 4). By this measure, alimentary sensations, hallucinations and emotions seemed to have relatively high repeatability when compared with movements or somæsthetic sensations.

There was no evidence that any of the mental phenomena was associated specifically with stimulation of either the dominant or non-dominant hemisphere.

In right-handed patients, stimulation of either temporal lobe was capable of evoking phenomena in each category, provided that that category had been evoked at least five times (Table 4). Furthermore, the distribution of all mental responses between the two hemispheres did not differ significantly (Table 4).

The widespread activation that occurred in response to electrical stimuli which evoked mental phenomena is further documented in Table 5. In 80 per cent of the occasions when an electrode was recorded during a mental phenomenon evoked by an ipsilateral stimulation, that electrode was either the stimulating electrode itself or it displayed an after-discharge or evoked potential during that stimulation. A high percentage was also obtained when applying the same analysis to individual electrode sites or individual categories of mental phenomena. On the other hand, no category of mental phenomena invariably required the activation of a particular structure, without requiring that other structures also be activated.

Table 6 makes a similar point. There is no apparent tendency for any category of mental phenomena to be evoked more easily from any particular site, once the general tendency for all mental phenomena to be more readily evoked by anterior structures as compared to more posterior structures is taken into account. Note also that a larger percentage of thalamic stimulations evoke mental phenomena than do medial temporal lobe stimulations ($\chi^2 = 32{\cdot}9$, df $= 1$, P, 2-tailed, $< 0{\cdot}001$). Furthermore, the mental phenomena evoked by thalamic stimulation are different than those evoked by medial temporal lobe stimulation ($\chi^2 = 10{\cdot}60$, df $= 1$, P, 2-tailed, $< 0{\cdot}005$), being restricted to simple somæsthetic and, perhaps, alimentary sensations (Table 6). Even within these categories, the sensations evoked by thalamic stimulation seemed to be more discrete than those evoked by medial temporal stimulation. For example, of 36 medial temporal lobe electrodes where stimulation yielded a somæsthetic sensation, only 10 yielded sensations that were lateralized to one side of the body, and these were about equally ipsilateral (6) and contralateral (4). In contrast, all 6 centre median electrodes whose stimulation induced somatic sensations yielded lateralized responses. In all cases, the responses were contralateral to the stimulating electrode.

In contrast to the apparent independence of category of mental phenomena from the anatomical site stimulated, examination of Table 7 indicates that the frequency of different categories of mental phenomena varies greatly among the patients. In any given patient, most mental phenomena were confined to one or two categories, and most of the reports in any single category were obtained from three or fewer patients. The hypothesis that the category of mental phenomenon elicited was related to *whom* one was stimulating, but not *where* (within the mesial temporal lobe), was tested using the χ^2 statistic.

First, the expected frequency of the individual cells was increased by combining categories as follows: Ht+Al, Mo, Hd+C+L+WB, T, SI, DV, Au, V, D+Me+OH, and E. The evoking of a seizure may imply a tendency toward hypersynchrony in a particular anatomical structure or patient, but gives no information regarding what mental function may be particularly associated with that structure or patient

TABLE 5. SITES ACTIVATED DURING STIMULUS-TRAINS EVOKING MENTAL PHENOMENA[1]

Electrode location[2]	Mental category																				
	Ht	*Al*	*Mo*	*Hd*	*C*	*L*	*WB*	*T*	*SI*	*DV*	*V*	*Au*	*D*	*Me*	*OH*	*E*	*Ae*	*Cf*	*Sz*	*U*	*Total*
Am	5/5	$\frac{44}{50}$	$\frac{6}{10}$	$\frac{9}{15}$	$\frac{10}{11}$	$\frac{11}{13}$	6/6	$\frac{12}{12}$	6/7	$\frac{17}{18}$	5/6	$\frac{12}{15}$	8/8	$\frac{25}{33}$	4/4	$\frac{13}{24}$	5/5	8/8	4/5	$\frac{13}{18}$	$\frac{164}{211}$
AHC	3/3	$\frac{49}{50}$	$\frac{9}{14}$	$\frac{13}{17}$	$\frac{12}{12}$	$\frac{14}{17}$	6/7	$\frac{15}{15}$	5/8	$\frac{16}{17}$	5/9	$\frac{16}{17}$	8/8	$\frac{27}{32}$	5/5	$\frac{27}{28}$	9/9	$\frac{14}{14}$	8/8	$\frac{17}{21}$	$\frac{208}{239}$
MHC	2/2	$\frac{30}{32}$	$\frac{10}{12}$	$\frac{9}{12}$	$\frac{12}{12}$	$\frac{13}{15}$	4/5	$\frac{13}{13}$	5/6	4/4	6/9	$\frac{9}{13}$	8/8	$\frac{17}{22}$	4/4	$\frac{12}{12}$	7/7	$\frac{11}{11}$	6/6	6/8	$\frac{137}{161}$
PHC	5/5	$\frac{32}{40}$	$\frac{9}{11}$	$\frac{9}{14}$	7/8	$\frac{12}{16}$	3/4	8/9	5/6	$\frac{10}{11}$	1/6	4/6	7/7	$\frac{6}{18}$	2/2	$\frac{14}{19}$	9/9	9/9	4/5	$\frac{5}{12}$	$\frac{118}{170}$
AHCG	3/3	$\frac{24}{25}$	$\frac{5}{10}$	$\frac{7}{11}$	6/7	$\frac{14}{16}$	3/4	$\frac{7}{10}$	4/7	$\frac{11}{11}$	4/8	$\frac{8}{12}$	7/7	$\frac{17}{22}$	1/1	$\frac{19}{20}$	6/6	9/9	3/4	5/7	$\frac{125}{159}$
MHCG	4/4	$\frac{47}{53}$	$\frac{10}{14}$	$\frac{13}{17}$	$\frac{10}{11}$	$\frac{13}{16}$	6/7	$\frac{9}{14}$	4/7	$\frac{16}{16}$	4/9	$\frac{13}{17}$	9/9	$\frac{23}{31}$	5/5	$\frac{26}{28}$	9/9	$\frac{13}{13}$	6/6	$\frac{16}{19}$	$\frac{193}{235}$
PHCG	4/4	$\frac{34}{36}$	$\frac{6}{10}$	$\frac{13}{16}$	$\frac{10}{10}$	$\frac{11}{15}$	3/3	8/8	5/6	$\frac{11}{11}$	1/6	3/6	6/6	$\frac{17}{24}$	1/1	$\frac{9}{17}$	7/7	$\frac{12}{13}$	4/4	$\frac{8}{14}$	$\frac{133}{176}$
Un	0/0	1/1	1/1	0/3	0/0	0/0	0/0	0/0	1/1	2/3	0/0	1/2	3/3	$\frac{9}{14}$	0/0	0/0	0/0	4/4	0/0	2/3	$\frac{20}{29}$
Total	$\frac{26}{26}$	$\frac{261}{287}$	$\frac{56}{82}$	$\frac{73}{105}$	$\frac{67}{71}$	$\frac{88}{108}$	$\frac{31}{36}$	$\frac{72}{81}$	$\frac{35}{48}$	$\frac{87}{91}$	$\frac{26}{53}$	$\frac{66}{88}$	$\frac{56}{56}$	$\frac{141}{196}$	$\frac{22}{22}$	$\frac{120}{148}$	$\frac{52}{52}$	$\frac{80}{81}$	$\frac{35}{38}$	$\frac{72}{102}$	$\frac{1098}{1380}$

[1] The denominator in each cell indicates the number of times from which the indicated site was recorded during mental phenomena of the indicated category. The numerator indicates the number of those recordings that exhibited an evoked-potential or after-discharge, or during which that electrode itself was stimulated. [2] Histological verification of the stereotaxic placement procedure was not available for PHC and Un electrodes. For key to abbreviations, *see* Table 1.

TABLE 6. STIMULATIONS (ELECTRODES) EVOKING MENTAL PHENOMENA: CATEGORY OF MENTAL PHENOMENON *vs* SITE OF STIMULATION.

Site stimulated[2]	*Mental category*																					
	Ht	*Al*	*Mo*	*Hd*	*C*	*L*	*WB*	*T*	*SI*	*DV*	*Au*	*V*	*D*	*Me*	*OH*	*E*	*Cf*	*Ae*	*Sz*	*U*	*Total stim.*	*Total responses*[1]
Am	3 (1)	16 (5)		2 (2)	2 (1)	3 (3)	2 (2)		3 (3)	8 (4)		2 (1)		16 (8)	2 (1)	3 (3)	1 (1)			6 (4)	684 (61)	54 (20)
AHC		20 (14)	3 (3)	6 (4)	8 (7)	6 (4)	4 (3)	11 (7)	3 (3)	7 (3)	10 (5)	5 (3)	2 (2)	1 (1)	3 (3)	5 (5)	6 (6)	3 (3)	4 (3)	12 (7)	671 (67)	82 (36)
MHC		8 (6)	1 (1)	3 (3)	3 (3)	4 (2)	1 (1)	1 (1)	2 (2)		2 (2)	2 (1)		6 (2)	1 (1)	4 (2)	2 (2)	1 (1)	1 (1)		406 (50)	34 (18)
PHC		4 (1)	2 (2)			1 (1)	2 (2)				1 (1)							1 (1)		2 (2)	359 (40)	12 (6)
AHCG		3 (3)	2 (1)	2 (1)	1 (1)	2 (2)		1 (1)		1 (1)	3 (3)		2 (1)	6 (5)		18 (4)	4 (3)	2 (2)	2 (2)	1 (1)	441 (44)	40 (18)
MHCG	2 (2)	8 (3)	5 (3)	3 (3)		1 (1)		2 (2)		2 (2)			5 (3)	3 (3)		5 (2)	3 (3)	3 (2)	1 (1)		512 (56)	35 (16)
PHCG				1 (1)						1 (1)	1 (1)			2 (1)			1 (1)		1 (1)	1 (1)	382 (45)	7 (6)
Un			1 (1)											1 (1)			1 (1)				40 (4)	3 (3)
Total	5 (3)	59 (32)	14 (11)	17 (14)	13 (12)	17 (13)	9 (8)	15 (11)	8 (8)	19 (11)	17 (12)	9 (5)	9 (6)	35 (21)	6 (5)	35 (16)	18 (17)	10 (9)	9 (8)	22 (15)	3495 (367)	267 (123)
Thalamic		6 (1)		28 (3)	8 (2)	18 (4)	1 (1)												1 (1)	1 (1)	221 (13)	41 (8)

[1] This total is usually less than the sum obtained by simple addition of the numbers in the same row because stimulations (electrodes) which evoked mental phenomena lying in more than one category were only counted once in the 'total responses'. [2] Histological verification was not available for PHC, Un or thalamic electrodes. For keys to abbreviations, *see* Tables 1 and 2

TABLE 7. STIMULATIONS EVOKING MENTAL PHENOMENA: CATEGORY OF MENTAL PHENOMENON *VS* PATIENT STIMULATED

Patient stimulated	*Mental category*																				*Total responses*[1]	*Total responses less Cf, Ae, Sz, U*[1]	*Total stimulations*
	Ht	*Al*	*Mo*	*Hd*	*C*	*L*	*WB*	*T*	*SI*	*DV*	*Au*	*V*	*D*	*Me*	*OH*	*E*	*Cf*	*Ae*	*Sz*	*U*			
11								1	1							21	3				24	22	125
13									1					2		1			2	1	6	4	144
15																				1	1	0	149
16		12	1	4				1		1			1	9						8	34	26	125
17																					0	0	356
18		3	1								3	3				1				2	10	8	188
19																					0	0	112
20				2																	2	2	124
21	1	2	3	1	1		1	5													10	10	89
22		2	1	5	2	7	1	1			2						1		1		20	18	116
24																					0	0	86
26			1																		1	1	105
27																					0	0	54
28																					0	0	53
29		3															1	1	1		4	3	73
30	1							1				1	1		1	2		1			3	3	65
31					1														2		3	1	82
32		11		1		2					1			1	2	4		1			16	16	79
34		5	3	1	1	3	2	3	1		2					3	2	1			18	17	74
35																	3			1	4	0	66
36	3	8				3				6			1	1		1	2	4			17	14	82
38		1			1							2					1	1		1	5	3	92
43			2	1		1						3									7	7	62
44					1			2													3	3	50
48		4			4												1	1		1	6	4	75
49		1		2			3			10	6		3	14	1		1			4	33	31	155
51		1	1		1			1	2		3										6	6	53
52																			1		1	0	57
53		1								1			2	8		2					11	11	61
55		3																			3	3	93
57					1		1								2						3	3	63
59		1							2				1							1	5	4	55
61																	2				2	0	122
62		1							1	1							1			2	4	3	55
63			1			1	1														3	3	100
68																			2		2	0	55
Total	5	59	14	17	13	17	9	15	8	19	17	9	9	35	6	35	18	10	9	22	267	226	3495

---

[1] This total is usually less than the sum obtained by simple addition of the numbers in the same row because stimulations which evoked mental phenomena lying in more than one category were only counted once in the 'total responses' For key to abbreviations, *see* Table 2

Similarly, confusion and amnesia constitute relatively global disruptions of thinking that are nearly always accompanied by widespread after-discharges within the ipsilateral temporal lobe (Table 6). These categories thus seemed *a priori* to depend on the strength of the electrographic response rather than upon the particular patient or location stimulated, and therefore they were excluded from this analysis. Unclassified reports of mental phenomena were also not included. In order to assure the independence of the different observations, each electrode (rather than each stimulus train) was considered to constitute an individual observation. An electrode was classified under a certain category of mental phenomena if at least one of the stimulations of that electrode elicited that category. If more than one category of mental phenomena was evoked by stimulation of the same electrode, it was classified under the category which occurred with the largest number of stimulations. In this manner, Tables were constructed of (amalgamated) category of mental phenomena *versus* site stimulated, and (amalgamated) category *versus* patient stimulated, and χ^2 was evaluated for each Table. Since the expected cell frequencies were still too small for the direct application of the χ^2 test (Siegel, 1956), a modification (Haldane, 1939) giving the exact variance and expected mean of χ^2 for tables with small expected frequencies was used. This test confirmed the hypothesis that the category of mental phenomena obtained was related to the particular patient stimulated ($\chi^2 = 386{\cdot}9$, $E(\chi^2) = 227{\cdot}3$, $V(\chi^2) = 411$, $Z = 7{\cdot}87$, 2-tailed $P < 0{\cdot}005$) and failed to find any relation between anatomical site stimulated and mental phenomenon obtained ($\chi^2 = 43{\cdot}7$, $E(\chi^2) = \chi^2 = 54{\cdot}6$, $V(\chi^2) = 101{\cdot}0$, $Z = 1{\cdot}08$, 2-tailed $P = 0{\cdot}28$).

One possible factor responsible for the relation between the category of evoked mental phenomena and the patient stimulated may be the personality of the patient. We reasoned that if this were true, then patients who experienced fear or anxiety (Category E) may score higher on the 'psychæsthenia' (Pt) subscale of the Minnesota Multiphasic Personality Inventory (MMPI). This expectation was confirmed at the 0·05 level by the Mann-Whitney U test (Siegel, 1956) applied to the 20 patients for whom MMPI scores were available. Similarly, patients with memory-like or dream-like hallucinations scored higher ($P < 0{\cdot}01$) on the 'schizophrenia' (Sc) subscale.

Relation of Mental Phenomena to Epileptic Pathology

The proportion of stimulations which evoked mental phenomena similar to the patient's aura varied among the different categories (Table 4). Somatic sensations (Hd, L, WB), movements (Mo) and hallucinations (D, Me, OH) were almost never similar to auras, whereas alimentary sensations (Al) and emotions (E) often were. *Déjà vu* (DV) nearly always occurred in patients who experienced *déjà vu* as part of their aura.

When all evoked mental phenomena similar to the patients' spontaneous auras are considered together, they constitute 35 per cent of the mental phenomena evoked by stimulation of the temporal lobe ipsilateral to spontaneous clinical seizure onset ('diseased lobe'), but only 17 per cent of mental phenomena reported during stimulation of the contralateral temporal lobe ($\chi^2 = 8{\cdot}78$, df $= 1$, 2-tailed $P < 0{\cdot}01$). However, the number of *patients* who reported an aura-like mental phenomenon upon stimulation of their diseased temporal lobe was equal to the number who reported an aura-like mental phenomenon upon stimulation of the non-diseased lobe. Of 15 patients who reported an aura-like mental phenomenon upon stimulation, 2 had bilateral foci, 7 reported aura-like mental phenomena upon stimulation of either hemisphere, and 3 reported aura-like mental phenomena upon stimulation of only the *non*-diseased hemisphere. Sixty-eight per cent of the stimulations which evoked mental phenomena similar to the stimulated patient's spontaneous aura also evoked an after-discharge, whereas only 27 per cent of other evoked mental phenomena were accompanied by after-discharges ($\chi^2 = 33{\cdot}8$, df = 1, 2-tailed $P < 0{\cdot}001$).

The proportion of all stimulations of the diseased temporal lobe which evoked mental phenomena was smaller (6·4 per cent *vs* 8·9 per cent) than the proportion for the contralateral side ($\chi^2 = 6{\cdot}11$, df = 1, 2-tailed $P < 0{\cdot}02$). When a unilateral after-discharge was evoked, it more commonly led to amnesia if it occurred in the non-diseased lobe (7/35) than if it occurred in the diseased lobe (2/67) ($\chi^2 = 8{\cdot}26$, df = 1, 2-tailed $P < 0{\cdot}01$).

DISCUSSION

Categories of Mental Phenomena Reported

Most of the mental phenomena reported by our patients during temporal lobe stimulation could be categorized as a hallucinated image or scene, an emotion, usually fear or anxiety, a visceral sensation, usually epigastric, or an unformed sensory sensation (visual, auditory, or somæsthetic). These mental phenomena correspond closely to those reported by patients in other extensive series of medial temporal lobe stimulation (Baldwin, 1960; Van Buren, 1961). Although Penfield and Jasper (1954) mainly stimulated the lateral temporal neocortex, the mental phenomena reported here were also similar in phenomenology and frequency to their observations. It is interesting to note, however, two mental phenomena which were not evoked in our patients. Olfactory sensations have occasionally been evoked by stimulation of the hippocampus or amygdala (Chapman, 1960; Jasper and Rasmussen, 1958; Pampiglione and Falconer, 1960; Van Buren, 1961); our patients did not report olfactory sensations. This correlates with the absence of unit changes in the human hippocampus, hippocampal gyrus, and basolateral amygdala during olfactory stimulation (Halgren, Babb, Rausch and Crandall, 1977).

Other authors (Ervin, Mark and Stevens, 1969; Heath and Mickle, 1960; King, 1961; Stevens, Mark, Ervin, Pacheco and Suematsu, 1969) have provided detailed descriptions of a small number of patients who experienced long-lasting intense feelings of 'rage' or of well-being after temporal lobe stimulation. In accord with the findings of most other authors (for example, Mullan and Penfield, 1959), these feelings, and the equally long-lasting electrographic changes that accompanied them, did not occur in our series. Only one of nearly 3500 stimulations was associated with even a controllable feeling of anger. Perhaps this contrasting result was due to differences in the patient populations; aggression has been reported to be evoked only in 'aggressive patients' (Kim and Umbach, 1973) and intense pleasure only in patients under intense pain (Heath, John and Fontana, 1968). We did not implant electrodes in patients with these characteristics because of their poor prognosis of tolerating or benefiting from the implant procedure within our programme. However, it also should be noted that even in a study of patients implanted with electrodes primarily to control 'assaultive behaviour' possibly resulting from psychomotor epilepsy, no aggressive feelings could be evoked by stimulation of the amygdala (Chapman, 1960). An alternative explanation for the lack of long-lasting mental changes in our patients may lie in the stimulus configuration. We used exclusively the Lilly wave-form, which consists of two short pulses of opposite polarity (*see* Methods). Sem-Jacobsen (1968), based on very broad experience with different wave-forms, concluded that long-lasting mental or EEG changes are *only* evoked by monophasic stimuli at current levels high enough to cause tissue damage. Heath's group has reported obtaining strong, long-lasting emotional responses with both monophasic and biphasic stimulation using a variety of wave-forms. However, in order to obtain a clinical response using the Lilly wave-form, Heath and Mickle (1960) reported that a current of 70 mA was necessary. Subsequent studies (Brown, Babb, Soper, Lieb, Ottino and Crandall, 1977; Pudenz, Bullara, Jacques and Hambrecht, 1975) have indicated that the charge density necessary to pass this large current would probably result in tissue damage, regardless of the wave-form used.

One behaviour which was noted in this study and has only been occasionally reported by other studies (Feindel, 1961; Jasper and Rasmussen, 1958) was non-ictal motor phenomena. Most of these reports in our study were of dubious validity, given the high spontaneous rate one may expect of twitches, especially in an expectant patient. Interpretation of these responses as false-positives is consistent with the low level of repeatability of reports in this category, as compared with mental phenomena in other categories. It is also possible, however, that the motor activity was related to the temporal lobe stimulation. In rat, cat, and rhesus monkey, direct projections exist from the central nucleus of the amygdala to the pontine and mesencephalic tegmentum (Hopkins, 1975). Localized lesions of this amygdaloid nucleus in rats results in a permanent motor inco-ordination (Box and Mogenson, 1975). Disruption of motor activity has also been reported during stimulation of the rat dentate gyrus (Bland and Vanderwolf, 1972). It is possible that the implied motor involvement of the medial temporal lobe would only be expressed during stimulation as a disruption of ongoing motor activity, and thus, since our patients were stationary at stimulus onset, we would not have observed the motor effect.

Comparison with Effects of Stimulating Specific Sensory Areas

The somæsthetic sensations evoked by stimulation in the region of the centre median nucleus in our study were more discrete, simple, consistent and repeatable than those evoked by medial temporal lobe stimulation. It seems likely that sensations were evoked by presumed centre median stimulation when current spread to the adjacent (Talairach *et al.*, 1957) nucleus ventralis posterior lateralis thalami, the specific somæsthetic relay nucleus. These contrasts are even clearer when the characteristics reported here of medial temporal lobe stimuli which evoked mental phenomena are compared with the characteristics reported elsewhere for stimulation of the primary visual or somatosensory cortex. Sensations may be evoked from primary sensory cortex with relatively weak stimuli, whereas stimuli that did not evoke widespread responses or after-discharges were seldom effective in the medial temporal lobe. Stimulation of electrodes only a few millimeters apart in primary sensory cortex will reliably evoke sensations that are distinguishable in a predictable manner (Brindley and Lewin, 1968; Dobelle, Mladejovsky and Girvin, 1974; Pollen, 1975), whereas medial temporal lobe stimulations centimetres apart often evoked the same mental phenomenon. Stimulation of a given anatomical locus within primary sensory cortex will evoke similar sensations in a very reliable manner from patient to patient (Brindley and Lewin, 1968; Dobelle *et al.*, 1974; Libet *et al.*, 1964; Pollen, 1975), whereas stimulation of a given anatomical site in the medial temporal lobe usually evoked no mental phenomenon. If one was evoked, it may have belonged to any of a wide variety of categories. Clearly, these strong contrasts between the mental effects of primary sensory cortex *versus* medial temporal lobe stimulation imply that different mechanisms are involved in their production.

In considering this mechanism by which mental phenomena are evoked, we must first realize that every mental phenomenon occurs within a total experience (James, 1890) that probably has a diffuse, widespread cortical substrate. Even reported elementary sensations are interpreted verbally and nonverbally, cognitively and emotionally, with respect to remembered instructions, and to previously and simultaneously occurring sensations of different modalities. The context of the mental phenomenon may also include unrelated emotions, cognitions, and sensations. The study of disconnection syndromes in humans has indicated that these varied processes can only be applied to information that has anatomical access to widespread cortical areas (Geschwind, 1965*a*, *b*; Sperry, 1974). The total experience within which an evoked mental phenomenon occurs must therefore have a diffuse neural representation. Stimulation of the specific sensory cortex apparently only determines the elementary sensation evoked; as with natural stimulation, the interpretative and other mental phenomena comprising the total experience may vary from stimulation to stimulation. Indeed, we may speculate that because elementary sensations ordinarily occur under natural conditions only when a restricted locus on the receptor surface (retina or skin) is stimulated, and the neural projections of these receptors remain spatially restricted for several synapses before significantly dispersing to other cortical regions, that stimulation of these projections before they disperse would evoke a similar sensation to stimulating the associated receptor surface. In other words, direct electrical activation of sensory cortex neurons *imitates* the neural, and thus the mental, consequences of an elementary sensory stimulus.

In contrast, the types of mental phenomena which were reported by our patients during temporal lobe stimulation would not ordinarily be associated with a restricted locus on a sensory surface or with any other single determinant. For example, fear may be evoked by sensory stimuli of all modalities and degrees of complexity, by visceral events, by memories, and by hormonal changes. There is no reason to suppose, then, that its neuronal representation is all connected, more or less directly, with a restricted cortical locus, as there is for a visual phosphene, which has a very restricted determinant. Furthermore, hallucinations of complete scenes, emotional states such as fear, and cognitive interpretations of the present environment, such as *déjà vu*, are more global than simple sensations, in the sense that they specify more of the content of an experience. For example, an hallucinated scene not only determines much more of the visual field than does a visual phosphene, it also is often accompanied by related sensations in other modalities, by appropriate emotions, or by a characteristic cognitive interpretation and restriction of attention. That is, the neural substrate of an evoked hallucination involves more cognitive abilities and thus presumably is more diffuse cortically than the neural substrate of an elementary sensation. The problem of describing how temporal lobe stimulation evokes mental experience is thus one of determining how a punctate electrical stimulus can activate a diffuse set of neurons that we have no reason to believe are pre-connected to any discrete anatomical locus.

Mechanisms through which Electrical Stimulation may Evoke Mental Phenomena

There appears to be two possible mechanisms that may work alone or in combination when medial temporal lobe stimulation activates these diffuse circuits. The widespread neuronal response to electrical stimulation may temporarily prevent the medial temporal lobe from performing its normal processing and transformations of neuronal activity. In addition to the directly resulting deficits observable behaviourally, monitoring by the remaining intact brain may result in a report of the lost mental processes, or may by interacting with ongoing processes indirectly evoke other mental phenomena. Amnesia and confusion, which usually, in our experience, were associated with after-discharges, may be examples of incapacitation. On the other hand, electrical stimulation may antidromically, orthodromically, and transynaptically excite neural elements afferent and efferent to the medial temporal lobe. Mental phenomena evoked in this fashion may in some sense represent a caricature of medial temporal lobe function. For example, bilateral lesions of the hippocampal formation in man are well known to severely impair the recall of recent memories (Milner, 1968). Recent evidence further suggests that some neurons in the hippocampal gyrus are activated during the recall and recognition of recent memory (Halgren, Babb and Crandall, 1978). A greatly increased outflow from the hippocampal gyrus, such as may occur with medial temporal lobe stimulation, may then be interpreted by the rest of the brain as an extreme feeling of recognition for all present stimuli, or *déjà vu*.

It seems likely that the visceral sensations evoked in our patients were also due to a direct activation of the neural networks associated with such sensations. Both the hippocampus (Valenstein and Nauta, 1959) and the amygdala (Dreifuss, 1972; de Olmos, 1972) project strongly to hypothalamic areas involved in food regulation, and units in both areas are influenced by electrical stimulation of the vagal nerve (Radna and MacLean, 1976). An alternative possibility is that these visceral sensations were evoked indirectly Viscero-*motor* responses to hippocampal formation and amygdala stimulation have been observed in animals (Kaada, 1951, 1972). However, a study by Van Buren (1963) reported that autonomic sensations evoked by medial temporal lobe stimulation in humans are usually *not* associated with observable modifications of visceral activity.

Unformed Visual Hallucinations

The unformed visual sensations evoked by medial temporal lobe stimulation probably did not result from spread of current to the optic tract, which lies immediately medial to the temporal lobe, nor to the optic radiation, one arm of which (the loop of Meyer: Crosby, Humphrey and Lauer, 1962) courses in the white matter relatively close to the posterior hippocampal gyrus. First, there was no predilection in our study for unformed visual responses to be localized to posterior structures. Second, Adams and Rutkin (1970), who stimulated both the visual radiation and the hippocampal formation, found clear differences in the types of visual sensations evoked from the two areas; visual radiation stimulation evokes simple visual sensations (i.e., phosphenes) whereas hippocampal stimulation evokes unformed visual sensations (e.g., coloured balls, flashing lights) similar to those reported here.

Furthermore, clear anatomical and physiological evidence exists for visual input to the hippocampal formation and amygdala of animals and humans. In the squirrel monkey, units are found in the hippocampal gyrus posterior to the entorhinal cortex (areas TF and TH of von Bonin and Bailey, 1947), that respond to flashes and to tonic visual stimulation. Areas TF and TH receive direct connections from the lateral geniculate body, inferior pulvinar nucleus (MacLean and Creswell, 1970), circumstriate cortex, and inferotemporal cortex (Jones and Powell, 1970). Areas TF and TH project to the entorhinal cortex (Van Hoesen and Pandya, 1975) which in turn projects to the hippocampus. The inferotemporal cortex may also provide visual input via its direct projections to the amygdala and to the perirhinal cortex (Jones and Powell, 1970; Van Hoesen and Pandya, 1975). The perirhinal cortex in turn sends fibres to the entorhinal cortex and hippocampus (Van Hoesen and Pandya, 1975; Seltzer and Pandya, 1976). MacLean (1975) failed to find neurons responsive to flashes in the entorhinal cortex, hippocampus, or amygdala of squirrel monkeys. However, such responses have been reported to occur in humans by Babb, Halgren and Crandall (1976). Responses were especially frequent in the posterior hippocampal gyrus. Thus, it seems likely that the unformed visual sensations reported by our patients were due to activation of medial temporal lobe areas intimately related to visual perception, rather than from current spread directly exciting the optic tract or radiation.

Complex Hallucinations

The hallucinations of visual scenes reported by our patients may have resulted from an interaction between the disruptive and the activating effects of temporal lobe stimulation. Penfield and Perot (1963), whose patients reported similar hallucinations upon temporal stimulation, considered the hallucinations to arise exclusively via an *activation* of temporal lobe-centrencephalic circuits associated with a specific memory. Mahl *et al.* (1964) in contrast, suggested on the basis of a single patient that hallucinations were evoked when temporal lobe stimulation disrupted normal cognitive mentation orientated toward reality (in Freudian terms, secondary process), thus permitting images representing current psychological concerns (or primary process) to emerge into consciousness, in a manner analogous to dreaming. Horowitz *et al.* (1968) offer a more general formulation, suggesting that temporal lobe stimulation may induce a state of mind favourable for the experience and reporting of internally generated images, no matter what the source—memory, emotional concerns, or simple visual hallucinations simultaneously induced. Our observation that hallucinations of scenes were always accompanied by wide-spread disruption of medial temporal lobe electrical activity supports these theories in their postulation of a role of disruption in the ætiology of complex hallucinations induced by stimulation. Furthermore, hallucinations which were described by our patients as like a dream, cartoon, or television programme, were more likely to be associated with after-discharges than were other hallucinations, described as like a memory. This observation suggests that the degree of perceived unreality associated with an hallucination is partially a function of the degree of temporal lobe disruption.

Our studies do not indicate areas in which it is critical for disruption to occur in order that a hallucination will be evoked. It is interesting, however, to note that two other conditions associated with hallucinations, natural dreaming and LSD, are also associated with a profound disruption of hippocampal neuronal activity. Hallucinations and other effects of LSD (Grof, 1975; Masters and Houston, 1967; Siegel and Jarvik, 1975) appear to be similar in several respects to those evoked by temporal lobe stimulation. This phenomenological similarity implies that, although differing in primary mechanism, these hallucinations may ultimately be correlated with similar brain states. After low to moderate doses of LSD, the hippocampal EEG displays an often profound flattening interspersed with paroxysmal waves in rabbits (Baran and Longo, 1964; Brucke, Gogolak and Stumpf, 1961), cats (Adey, 1969), and humans (Chapman, Walter, Adey, Crandall, Rand, Brazier and Markham, 1962; Monroe, Heath, Mickle and Llewellyn, 1957). Hippocampal unit activity displays parallel changes in rabbits. Most hippocampal neurons in rats (Ranck, 1973) and in humans (Ravagnati, Halgren, Babb and Crandall, 1977) are also profoundly inhibited during paradoxical sleep, which, at least in humans, is characterized by vivid visual hallucinations (Freemon, 1972). The temporal lobe is not only profoundly affected during hallucinations, it may also be necessary for their occurrence. The behaviours which suggest that chimpanzees hallucinate under LSD are no longer seen after bilateral temporal lobectomy (Baldwin, Lewis and Bach, 1959). In contrast, frontal lobectomy does not noticeably alter LSD-induced behaviour in chimpanzees (Baldwin *et al.*, 1959) or humans (Holden and Itil, 1970).

We may combine these two lines of evidence, that the critical area disrupted during induced hallucinations is the hippocampus, and that these hallucinations emerge as a result of disrupted control by reality-orientated cognition over mental contents, into the speculation that the hippocampus functions normally in some aspect of this control. This speculation appears to be at least consistent with several other bodies of evidence. As reviewed by Douglas (1967), most hypotheses of hippocampal function derived from animal experiments assign it a role in the inhibition of various processes, including attentional or motivational responses to stimuli (internal inhibition: Douglas, 1975), and inappropriate behavioural hypotheses (Kimble, 1975). An involvement in 'control' is also suggested by the strong projection of the prefrontal cortex, which seems to have an executive role in behaviour (Luria, 1966; Nauta, 1971), to the hippocampus (Leichnetz and Astruc, 1975; Nauta, 1971; Van Hoesen, Pandya and Butters, 1975). Recently, human hippocampal neurons have been discovered which are most active during activities which, because of their complexity, painfulness, or transitional nature, appear to require greater conscious control for their execution (Halgren, Babb and Crandall, 1978).

Horowitz, Adams and Rutkin (1968) hypothesized that the hallucinations of formed images develop from the activation of unformed visual sensations (*see above*) on the background of a receptive mental state resulting from temporal lobe disruption. They proposed that the ongoing motivational dynamics of the patient would provide expected images, which would be chosen among, according to their concordance, with the unformed visual sensations. We also support a role for the neural circuits directly activated by temporal lobe stimulation in the selection of the hallucinated image. However, we propose that the directly activated circuits may be those underlying perception of formed visual images, as well as the unformed sensations discussed by Horowitz. This contention is supported by the powerful projections of visual association cortex to the hippocampal gyrus and amygdala and by the apparent responsiveness of neurons in these areas to specific visual images. Jacobs and McGinty (1972) and O'Keefe and Bouma (1969) have reported neurons in the basolateral nuclear complex of the cat amygdala that responded only to the sight of a mouse or rat, or to other complex sensory stimuli. Similarly, Halgren, Babb, and Crandall (1978) have observed a neuron in the human hippocampal gyrus that only fired when the patient was answering questions regarding his hospital room and ward. These considerations, and the observation that none of our patients reported that their hallucinations of complex images were preceded by, or developed out of, unformed visual hallucinations, suggests that the specific hallucination experienced may result, in part, from the direct activation by electrical stimulation of neuronal circuits associated with specific complex images. The image-circuits so activated may interact and overlap with other image-circuits activated as a result of the patients' ongoing emotional concerns. The resulting image, escaping suppression by an incapacitated hippocampus, may then be perceived.

Anxiety or Fear

As with hallucinations, both the disruption and the activation produced by stimulation of the medial temporal lobe may be involved in evoking the feelings of anxiety or fear reported by our patients. One may question whether the vast preponderance of anxiety or fear over other types of emotions implies that the medial temporal lobe is somehow a centre for this emotion. A consideration of current theories of anxiety suggests other possibilities. Many theories propose that anxiety arises in situations that pose a threatened dissolution of the ego (Fischer, 1970). If that were the case, then disruption of the medial temporal lobe would result in anxiety if it played an essential role in the normal functioning of the ego, at least in these patients. Alternatively, the direct and indirect excitation of hypothalamic and tegmental structures may be interpreted by the ego as unemployed libido which, according to Freudian theories, is responsible for 'neurotic' anxiety (that is, anxiety not related in a realistic manner to a specific external object or situation). Possibly this libido was related to a specific drive (aggression, hunger, sexual) which was not recognized because of the lack of a suitable object in the restricted environment in which the stimulation took place.

Various uncontrolled studies (reviewed by Robin and Macdonald, 1975) have reported that severing the connections between the frontal lobe and the dorsomedial thalamic nucleus, or severing the cingulum bundle, in man, results in a decrease in the intensity and frequency with which anxiety is experienced. Since both the cingulum bundle (White, 1959) and the dorsomedial thalamic nucleus (Krettek and Price, 1974; Lammers, 1972) possess reciprocal connections with the medial temporal lobe, it is interesting to speculate that some part of the frontal lobe may monitor the activity of the medial temporal lobe, and may respond to a disorganization and/or heightened level of such activity with a response that ultimately results in the experience of anxiety. This speculation is in line with other evidence assigning a monitoring role to the frontal lobes alluded to earlier. Perhaps the strongest conclusion that can be drawn from this variety of possible mechanisms is that, in our present state of ignorance of psychology and physiology, any conclusion regarding the localization of a complex behaviour is highly tentative at best.

Factors Selecting Mental Response

As noted above, the mental phenomena elicited by stimulation were usually associated with widespread disruption of the medial temporal lobe, were highly variable, and had low reproducibility. These characteristics suggested that the mental phenomena were evoked not by focal activation of a neuronal system but as result of a disruption of the function of the medial temporal lobe, and/or as a result of a partial activation of a diffuse neuronal system. The latter mechanisms do not postulate a direct activation of the neuronal substrate of some conscious experience, but rather that the ongoing activity of the rest of the brain is altered by the medial temporal stimulation, which in turn may or may not be significant enough to result in a change in the ongoing conscious contents. The direction of this change would be partially determined by the spontaneous neural patterns present at stimulus onset, which may be a function of the patients' ongoing concerns, his environmental situation, and the effects of previous stimulations. Another set of factors determining the type of mental phenomenon evoked would be the pathways by which the stimulation could affect the ongoing activity. These pathways could be relatively fixed, or could be partially a function of the patient's basic personality structure or his epileptic pathology. Most of the above factors would have large components specific to each patient. In contrast, the necessity for affecting large areas of tissue with the stimulation in order to evoke a mental phenomenon would suggest that the particular anatomical site stimulated in order to evoke the widespread disruption would be of relatively small importance. We may conclude that the characteristics of the stimulations evoking mental phenomena predicts, as we observed, that the significant variables determining whether a particular response was obtained would tend to be associated with the specific patient who was stimulated rather than with the anatomical locus of stimulation.

We can make no firm judgement as to which of the many variables associated with each patient was of greatest significance for selecting the evoked mental phenomenon. The physical environment in which the patients were stimulated was held constant from patient to patient, and so presumably was not a significant source of variability. The similar relative frequencies of different mental phenomena upon stimulation of the diseased as compared to the contralateral temporal lobe suggests that the epileptic pathology may also not have been a deciding factor. A possible exception may be *déjà vu*. Eighteen of the 19 *déjà vu* experiences occurred in patients who had previously experienced *déjà vu* as a part of their aura, but since in these patients *déjà vu* could be evoked from the non-diseased hemisphere without evoking potentials in the region of the contralateral focus, it seems unlikely that *déjà vu* was the result of secondary activation of this focus. Rather, the patients' predisposition to experience *déjà vu* must be viewed more generally, perhaps even as related to a personality structure that predisposed them to experience *déjà vu* as an aura.

In any case, the only patient-related variable which we observed to be clearly related to the type of mental phenomenon evoked was their scores on various subscales of the Minnesota Multiphasic Personality Inventory (MMPI). Patients who experienced evoked emotions, usually anxiety or fear, scored higher on the 'psychæsthenia' (pt) scale than other patients. A characteristic of the patients who were used in order to select items for the construction of this scale was their anxiety and tenseness (McKinley and Hathaway, 1956). Patients experiencing dream-like or memory-like hallucinations scored higher on the 'schizophrenia' scale. In view of the limitations of a true-false test in describing adequately a human personality, we consider it premature to deduce from these results the personality characteristics of patients who experience anxiety or hallucinations upon temporal lobe stimulation. This data does, however, provide preliminary evidence that such characteristics exist and suggests the directions in which they may be sought.

Clinical Usefulness

An aura-like mental phenomenon was evoked from the temporal lobe *contralateral* to the electrographic focus in as many patients as it could be evoked from the diseased lobe. This would seem to indicate that the evoking of an aura by electrical stimulation should *not* be used as a primary criterion for localizing the epileptic focus. However, since the percentage of the total number of evoked mental phenomena that were aura-like was higher in the diseased lobe, the evoking of an aura-like mental phenomenon may provide some lateralizing information, if both lobes are stimulated.

The lower frequency of all evoked mental phenomena upon stimulation of the diseased lobe as compared to the non-diseased lobe was not of sufficient magnitude to be of direct clinical relevance. This observation is of interest, however, in that it correlates with other studies of the same series of patients indicating a lower frequency of evoked potentials and after-discharges upon stimulation of the diseased lobe (Cherlow, Dymond, Crandall, Walter and Serafetinides, 1977), and a lower incidence of active neurons when recording from the diseased hippocampus as compared to the contralateral hippocampus (Babb and Crandall, 1976). The probable cause of this relative inexcitability appears to be the histologically demonstrable lack of neurons in areas affected by hippocampal sclerosis (Brown, 1973; the Scheibels, 1973).

The principal clinical goal of the more recent stimulations reported here was to evaluate the effect of unilateral after-discharges on memory function in order to gauge the contribution of the stimulated region to memory function. The presence of amnesia during an after-discharge confined to one temporal lobe would strongly indicate against the surgical removal of that lobe. Our findings were consistent with this clinical use of electrical stimulation; amnesia was demonstrable after unilateral after-discharges, particularly if the after-discharge occurred in the non-diseased temporal lobe.

SUMMARY

Of 3495 stimulations of the medial temporal lobe of 36 psychomotor epileptics, 267 were accompanied by reports of mental phenomena, including hallucinations of complete scenes, *déjà vu*, anxiety, visceral sensations, amnesia, and unformed sensory experiences. Olfactory and frankly aggressive responses were not observed. The factors selecting whether a particular stimulus would evoke a mental phenomenon, and which category of mental phenomena would be evoked, could be explored because of the similarity across patients of the anatomical loci and protocols of stimulation. In general, a widespread electrographic response was necessary but not sufficient for an experiential response to occur. That is, 89 per cent of evoked mental phenomena were accompanied by an evoked potential (EP) and/or after-discharge (AD), but only 10 per cent of those stimuli that evoked an EP and/or AD also evoked a mental phenomenon. In contrast, only 2 per cent of stimuli that evoked neither an EP nor AD evoked a mental phenomenon. Contralateral EPs were rare. Anterior electrode sites, and sites contralateral to the focus, had a higher frequency of both electrographic and mental responses. The category of mental phenomenon was not related to the anatomical site, however, but rather to patient-specific variables. Patients reporting fear scored higher on the 'psychæsthenia' subscale of the Minnesota Multiphasic Personality Inventory (MMPI), and patients experiencing hallucinations scored higher on the 'schizophrenic' subscale than did the other patients. Our findings suggest that, in contrast to the primary visual or somatosensory areas, where the evoked mental phenomena are highly predictable and are closely related to the anatomical site, the mental phenomena evoked by medial temporal lobe stimulation are idiosyncratic and variable, and are related to the personality of the patient stimulated.

ACKNOWLEDGEMENTS

We thank M. Walter, M. Sergi, and W. Reber for aid in tabulation and computation, S. Weingarten for participating in the operations, E. Mariani, E. Carr, J. Thompson, R. Smith, R. Hicks, and L. Mitchell for technical assistance, E. Modiest and J. Hopgood for preparation of the stimulation protocols and P. Suppes and T. Babb for useful critical comments on the manuscript. We are particularly indebted to G. Marsh, R. Rausch, and S. Smith-Neafsey for administering, scoring and collecting the MMPIs. This research was supported by USPHS grant NS 02808 to P.H.C., by a grant from the Ralph Smith Foundation, and by a post-doctoral fellowship to E.H. from the Bank of America—Gianini Foundation We acknowledge the active co-operation of our patients for making this research possible. Please address reprint requests to E. Halgren, BRI 73-364 CHS, UCLA, Los Angeles, California 90024, USA.

REFERENCES

ADAMS, J. E. and RUTKIN, B. B (1970) Visual responses to subcortical stimulation in the visual and limbic systems. *Confinia Neurologica*, **32**, 158–164.

ADEY, W. R. (1969) Neurophysiological actions of LSD: In: *Neurophysiological and Behavioral Aspects of Psychotropic Drugs.* Edited by A. G. Karczmar and W. P. Koella. Springfield, Illinois: Thomas, pp. 5-26.

ANGELERI, F., FERRO-MILONE, F. and PARIGI, S. (1964) Electrical activity and reactivity of the rhinencephalic, pararhinencephalic, and thalamic structures: Prolonged implantation of electrodes in man. *Electroencephalography and Clinical Neurophysiology*, **16**, 100–129.

BABB, T. L. and CRANDALL, P. H. (1976) Epileptogenesis of human limbic neurons in psychomotor epileptics. *Electroencephalography and Clinical Neurophysiology*, **40**, 225-243.

—— HALGREN, E. and CRANDALL, P. H. (1976) Visual receptive properties of human limbic neurons. *Neuroscience Abstracts*, **2**, 380.

BALDWIN, M. (1960) Electrical stimulation of the mesial temporal region. In: *Electrical Studies on the Unanesthetized Brain.* Edited by E. R. Ramey and D. S. O'Doherty. New York: Hoeber, pp. 159-176.

—— LEWIS, S. A. and BACH, S. A (1959) The effects of lysergic acid after cerebral ablation. *Neurology, Minneapolis*, **9**, 469–474.

BARAN, L. and LONGO, V. G. (1964) Instrumental reward discrimination in rabbits: EEG and behavioral effects of a series of lysergic acid derivatives. *Acta Physiologica Latinoamericana*, **14**, 125–137.

BICKFORD, R. G., MULDER, D. W., DODGE, H. W., SVIEN, H. J. and ROME, H. P. (1958) Changes in memory function produced by electrical stimulation of the temporal lobe in man. *Research Publications Association for Research in Nervous and Mental Disease*, **36**, 227-243.

BLAND, B. H. and VANDERWOLF, C. H. (1972) Electrical stimulation of the hippocampal formation. Behavioral and bioelectric effects. *Brain Research, Amsterdam*, **43**, 89–106.

BONIN, G. VON and BAILEY, P. (1947) *The Neocortex of Macaca Mulatta.* Urbana: University of Illinois Press.

BOX, B. M. and MOGENSON, G. J. (1975) Alterations in ingestive behaviors after bilateral lesions of the amygdala in the rat. *Physiology and Behavior*, **15**, 679–688.

BRAZIER, M. A. B. (1966) Stimulation of the hippocampus in man using implanted electrodes. In: *RNA and Brain Function, Memory and Learning*. Edited by M. A. B. Brazier. Berkeley: University of California Press, pp. 299–310.

BRINDLEY, G. S. and LEWIN, W. S. (1968) The sensations produced by electrical stimulation of the visual cortex. *Journal of Physiology*, **196**, 474–493.

BRODMANN, K. (1909) *Vergleichende Lokalisationstehre der Großhirnrinde*. Leipzig: Barth.

BROWN, W. J. (1973) Structural substrates of seizure foci. In: *Epilepsy · Its Phenomena in Man*. Edited by M. A. B. Brazier. New York: Academic Press, pp. 339–374.

—— BABB, T. L., SOPER, H. V., LIEB, J. P., OTTINO, C. A. and CRANDALL, P. H. (1977) Tissue reactions to long-term electrical stimulation of the cerebellum in monkeys. *Journal of Neurosurgery*, **47**, 366–379.

BRUCKE, F., GOGOLAK, G. and STUMPF, C. H. (1961) Die Wirkung von LSD auf die Makro-und Mikrotatigkeit des Hippocampus. *Naunyn-Schmiedeberg's Archiv fuer Experimentelle Pathologie und Pharmakologie*, **240**, 461–468.

CHAPMAN, L. F., WALTER, R. D., ADEY, W. R., CRANDALL, P. H., RAND, R. W., BRAZIER, M. A. B. and MARKHAM, C. H. (1962) Altered electrical activity of human hippocampus and amygdala induced by LSD. *Physiologist*, **5**, 118.

—— —— MARKHAM, C. H., RAND, R. W. and CRANDALL, P. H. (1967) Memory changes induced by stimulation of hippocampus or amygdala in epilepsy patients with implanted electrodes. *Transactions of the American Neurological Association*, **92**, 50–56.

CHAPMAN, W. P. (1958) Studies of the periamygdaloid area in relation to human behavior. *Research Publications Association for Research in Nervous and Mental Disease*, **36**, 258–277.

—— (1960) Depth electrode studies in patients with temporal lobe epilepsy. In: *Electrical Studies on the Unanesthetized Brain*. Edited by E. R. Ramey and D. S. O'Doherty. New York: Hoeber, pp. 334–350.

CHERLOW, D. G., DYMOND, A M., CRANDALL, P. H., WALTER, R. D. and SERAFETINIDES, E. A. (1977) Evoked response and after-discharge thresholds to electrical stimulation in temporal lobe epileptics. *Archives of Neurology*, **34**, 527–531.

CRANDALL, P. H. (1975) Post-operative management and criteria for evaluation. In: *Neurosurgical Management of the Epilepsies*. Edited by D. P. Purpura, J. K. Penry and R. D. Walter. New York: Raven Press, pp. 265–280.

—— WALTER, R. D. RAND, R. W. (1963) Clinical applications of studies of stereotactically implanted electrodes in temporal-lobe epilepsy. *Journal of Neurosurgery*, **21**, 827–840.

CROSBY, E. C. and HUMPHREY, T. (1941) Studies of the vertebrate telencephalon. II. The nuclear pattern of the anterior olfactory nucleus, tuberculum olfactorium, and the amygdaloid complex in adult man. *Journal of Comparative Neurology*, **74**, 309–352.

—— —— and LAUER, E. W. (1962) *Correlative Anatomy of the Nervous System*. New York: Macmillan, p. 279.

DOBELLE, W. H., MLADEJOVSKY, M. G. and GIRVIN, J. P. (1974) Artificial vision for the blind: Electrical stimulation of visual cortex offers hope for a functional prosthesis. *Science*, **183**, 440–444.

DOUGLAS, R. J. (1967) The hippocampus and behavior. *Psychological Bulletin*, **67**, 416–442.

DOUGLAS, R. J. (1975) The development of hippocampal function: implications for theory and for therapy. In: *The Hippocampus.* Volume 2. *Neurophysiology and Behavior.* Edited by R. L. Isaacson and K. H. Pribram. New York: Plenum, pp. 327–361.

DREIFUSS, J. J. (1972) The effects of electrical stimulation of the amygdaloid complex on the ventromedial hypothalamus. In: *The Neurobiology of the Amygdala.* Edited by B. E. Eleftheriou New York: Plenum, pp. 295–317.

ECONOMO, C. VON (1927) *Zellaufbau der Grosshirnrinde des Menshen.* Berlin: Springer.

ERVIN, F. R., MARK, V. H. and STEVENS, J. (1969) Behavioral and affective responses to brain stimulation in man. *Proceedings of the American Psychopathological Association,* **58,** 54–65.

FEINDEL, W. (1961) Response patterns elicited from the amygdala and deep temporoinsular cortex. In: *Electrical Stimulation of the Brain.* Edited by D. E. Sheer. Austin: University of Texas Press, pp. 519–532.

FERGUSON, S. M., RAYPORT, M., GARDNER, R., KASS, W., WEINER, H. and REISER, M. F. (1969) Similarities in mental content of psychotic states, spontaneous seizures, dreams, and responses to electrical brain stimulation in patients with temporal lobe epilepsy. *Psychosomatic Medicine,* **31,** 479–498.

FISCHER, W. F. (1970) *Theories of Anxiety.* New York: Harper and Row.

FREEMON, F. R. (1972) *Sleep Research: A Critical Review.* Springfield, Illinois: Thomas.

GESCHWIND, N. (1965*a*) Disconnection syndromes in man. I. *Brain,* **88,** 237–294.

—— (1965*b*) Disconnection syndromes in man. II. *Brain,* **88,** 585–644.

GROF, S. (1975) *Realms of the Human Unconscious: Observations from LSD Research.* New York: Viking.

HALDANE, J. B. S. (1939) The mean and variance of χ^2 when used as a test of homogeneity, when expectations are small. *Biometrika,* **31,** 346–355.

HALGREN, E., BABB, T. L. and CRANDALL, P. H. (1978) Activity of human hippocampal formation and amygdala neurons during tests of memory and movement. In press.

—— —— RAUSCH, R. and CRANDALL, P. H. (1977) Neurons in the human basolateral amygdala and hippocampal formation do not respond to odors. *Neuroscience Letters,* **4,** 331–335.

HEATH, R. G. (1964) Pleasure response of human subjects to direct stimulation of the brain: Physiologic and psychodynamic considerations. In: *The Role of Pleasure in Behavior* Edited by R. G. Heath. New York: Harper and Row, pp. 219–243.

—— JOHN, S. B. and FONTANA, C. J. (1968) The pleasure response: Studies by stereotaxic technics in patients. In: *Computers and Electronic Devices in Psychiatry.* Edited by N. Kline and E. Laska. New York: Grune and Stratton, pp. 178–189.

—— and MICKLE, W. A. (1960) Evaluation of seven years' experience with depth electrode studies in human patients. In: *Electrical Studies on the Unanesthetized Brain.* New York: Hoeber, pp. 214–248.

HOLDEN, J. M. C. and ITIL, T. (1970) The influences of the standard prefrontal lobotomy operation on hallucinatory phenomena associated with psychotomimetic drugs. In: *Origin and Mechanism of Hallucinations.* Edited by W. Keup. New York: Plenum, pp. 37–51.

Hopkins, D. A. (1975) Amygdalalotegmental projections in the rat, cat, and rhesus monkey. *Neuroscience Letters*, **1**, 263–270.

Horowitz, M. J., Adams, J. E. and Rutkin, B. B. (1968) Visual imagery on brain stimulation. *Archives of General Psychiatry*, **19**, 469–486.

Humphrey, T. (1972) The development of the human amygdaloid complex. In: *The Neurobiology of the Amygdala.* Edited by B. E. Eleftheriou. New York: Plenum, pp. 21–77.

Ishibashi, T., Hori, H., Endo, K. and Sato, T. (1964) Hallucinations produced by electrical stimulation of the temporal lobes in schizophrenic patients. *Tohoku Journal of Medicine*, **82**, 124–139.

Jacobs, B. L. and McGinty, D. (1972) Participation of the amygdala in complex stimulus recognition and behavioral inhibition. Evidence from unit studies. *Brain Research, Amsterdam*, **36**, 431–436.

James, W. (1890) *Principles of Psychology*, Volume 1, Chapter IX. New York: Henry Holt.

Jasper, H. H. and Rasmussen, T. (1958) Studies of clinical and electrical responses to deep temporal stimulation in man with some considerations of functional anatomy. *Research Publications Association for Research in Nervous and Mental Disease*, **36**, 316–334.

Jones, E. G. and Powell, T. P. S. (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, **93**, 793–820.

Kaada, B. R. (1951) Somato-motor, autonomic, and electrocorticographic responses to electrical stimulation of 'rhinencephalic' and other structures in primates, cat and dog. *Acta Physiologica Scandinavica*, **24**, Supplementum 83, 1–285.

—— (1972) Stimulation and regional ablation of the amygdaloid complex with reference to functional representations. In: *The Neurobiology of the Amygdala.* Edited by B. E. Eleftheriou. New York. Plenum, pp. 205–281.

Kim, Y. K. (1971) Effects of basolateral amygdalectomy. In: *Special Topics in Stereotaxis* Edited by W. Umbach. Stuttgart: Hippokrates-Verlag, pp. 69–81.

—— and Umbach, W. (1973) Combined and stereotaxic lesions for treatment of behavioral disorders and severe pain. In: *Surgical Approaches in Psychiatry.* Edited by L. V. Laitinen and K E. Livingston. Baltimore: University Park Press, pp. 182–195.

Kimble, D. P. (1975) Choice behavior in rats with hippocampal lesions. In: *The Hippocampus.* Volume 2. *Neurophysiology and Behavior.* Edited by R. L. Isaacson and K. H Pribram. New York: Plenum, pp. 306–326.

King, H. E. (1961) Psychological effects of excitation in the limbic system. In: *Electrical Stimulation of the Brain.* Edited by D. E. Sheer. Austin: University of Texas, pp. 477–486.

Krettek, J. E. and Price, J. L. (1974) A direct input from the amygdala to the thalamus and the cerebral cortex. *Brain Research, Amsterdam*, **67**, 169–174.

Lammers, H. J. (1972) The neural connections of the amygdaloid complex in mammals. In: *The Neurobiology of the Amygdala.* Edited by B. E. Eleftheriou. New York: Plenum, pp. 123–144.

Leichnetz, G. R. and Astruc, J. (1975) Preliminary evidence for a direct projection of the prefrontal cortex to the hippocampus in the squirrel monkey. *Brain, Behavior and Evolution*, **11**, 355–364.

Libet, B., Albers, W. W., Wright, E. W., Jr., Delattre, L. D., Levin, G. and Feinstein, B. (1964) Production of threshold levels of conscious sensation by electrical stimulation of human somatosensory cortex. *Journal of Neurophysiology*, **27**, 546–578.

LURIA, A. R. (1966) *Higher Cortical Functions in Man.* New York: Basic Books.

MCKINLEY, J. C. and HATHAWAY, S. R. (1956) Scale 7 (psychasthenia). In: *Basic Readings on the MMPI in Psychology and Medicine.* Edited by G. S. Welsh and G. Dahlstrom. Minneapolis: University of Minnesota Press, pp. 81-86.

MACLEAN, P. D. (1975) An ongoing analysis of hippocampal inputs and outputs: microelectrode and neuroanatomical findings in squirrel monkeys. In: *The Hippocampus.* Volume 1. *Structure and Development.* Edited by R. L. Isaacson and K. H. Pribram. New York: Plenum, pp. 177-211.

—— and CRESWELL, G. (1970) Anatomical connections of the visual system with limbic cortex of monkey. *Journal of Comparative Neurology,* **138,** 265-278.

MAHL, G. F., ROTHENBERG, A., DELGADO, J. M. R. and HAMLIN, H. (1964) Psychological responses in the human to intracerebral electrical stimulation. *Psychosomatic Medicine,* **26,** 337-368.

MASTERS, R. E. L. and HOUSTON, J. (1967) *The Varieties of Psychedelic Experience.* New York: Dell.

MILNER, B. (1968) Disorders of memory after brain lesions in man. *Neuropsychologia,* **6,** 175-291.

MONROE, R. R., HEATH, R. G., MICKLE, W. A. and LLEWELLYN, R. C. (1957) Correlation of rhinencephalic electrograms with behavior: A study on humans under the influence of LSD and mescaline. *Electroencephalography and Clinical Neurophysiology,* **9,** 623-642.

MULLAN, S. and PENFIELD, W. (1959) Illusions of comparative interpretation and emotion. *Archives of Neurology and Psychiatry, Chicago,* **81,** 269-284.

NAUTA, W. J. H. (1971) The problem of the frontal lobe: A reinterpretation. *Journal of Psychiatric Research,* **8,** 167-187.

O'KEEFE, J. and BOUMA, H. (1969) Complex sensory properties of certain amygdala units in freely moving cat. *Experimental Neurology,* **23,** 384-398.

OLMOS, J. S. DE (1972) The amygdaloid projection field in the rat as studied with the cupric-silver method. In: *The Neurobiology of the Amygdala.* Edited by B. E. Eleftheriou. New York: Plenum, pp. 145-204.

PAMPIGLIONE, G. and FALCONER, M. A. (1960) Electrical stimulation of the hippocampus in man. In: *Handbook of Physiology.* Section 1. *Neurophysiology,* Volume 2. Edited by J. Field, H. W. Magoun, and V. E. Hall. Washington, D.C.: American Physiological Society, pp. 1391-1394.

PENFIELD, W. P. (1958) Functional localization in temporal and deep Sylvian areas. *Research Publications Association for Research in Nervous and Mental Disease,* **36,** 210-226.

—— and JASPER, H. (1954) *Epilepsy and the Functional Anatomy of the Human Brain.* Boston: Little, Brown.

—— and PEROT, P. (1963) The brain's record of auditory and visual experience. A final summary and discussion. *Brain,* **86,** 595-696.

POLLEN, D. A. (1975) Some perceptual effects of electrical stimulation of the visual cortex in man. In: *The Nervous System.* Volume 2. *The Clinical Neurosciences.* Edited by T. N. Chase. New York: Raven, pp. 519-528.

PUDENZ, R. H., BULLARA, L. A., JACQUES, S. and HAMBRECHT, F. T (1975) Electrical stimulation of the brain. III. The neural damage model. *Surgical Neurology,* **4,** 389-400.

RADNA, R. J. and MACLEAN, P. D. (1976) Effects of vagal volleys on unit activity of amygdala, hippocampus, and corpus striatum in squirrel monkeys (*Saimiri Sciurens*). *Neuroscience Abstracts*, **2**, 374.

RANCK, J. B., Jr. (1973) Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. Part I. Behavioral correlates and firing repertoires. *Experimental Neurology*, **41**, 461-531.

RAVAGNATI, L., HALGREN, E., BABB, T. L. and CRANDALL, P. H. (1977) Activity of human hippocampal formation and amygdala neurons during sleep. *Neuroscience Abstracts*, **3**, 471

RAYPORT, M. and FERGUSON, S. M. (1974) Qualitative modification of sensory responses to amygdaloid stimulation in man by interview content and context. *Electroencephalography and Clinical Neurophysiology*, **34**, 714.

ROBIN, A. and MACDONALD, D. (1975) *Lessons of Leucotomy*. London: Kimpton.

SCHEIBEL, M. E. and SCHEIBEL, A. B. (1973) On hippocampal pathology in temporal lobe epilepsy. A Golgi survey. In: *Epilepsy: Its Phenomena in Man*. Edited by M. A. B. Brazier. New York: Academic Press, pp. 311-337.

SELTZER, B. and PANDYA, D. N. (1976) Some cortical projections to the parahippocampal area in the rhesus monkey. *Experimental Neurology*, **50**, 146-160.

SEM-JACOBSEN, C. W. (1968) *Depth Electrographic Stimulation of the Human Brain and Behavior*. Springfield, Illinois: Thomas.

—— and TORKILDSEN, A. (1960) Depth recording and electrical stimulation in the human brain. In. *Electrical Studies on the Unanesthetized Brain*. Edited by E. R. Ramey and D. S. O'Doherty. New York: Hoeber, pp. 275-290.

SERAFETINIDES, E. A., WALTER, R. D. and CHERLOW, D. G. (1975) Amnestic confusional phenomena, hippocampal stimulation, and laterality factors. In: *The Hippocampus*. Volume 2. *Neurophysiology and Behavior*. Edited by R. L. Isaacson and K. H. Pribram. New York: Plenum, pp. 363-375.

SIEGEL, R. K. and JARVIK, M. E. (1975) Drug-induced hallucinations in animals and man. In: *Hallucinations: Behavior, Experience, and Theory*. Edited by R. K. Siegel and L. J. West. New York: Wiley, pp. 81-161.

SIEGEL, S. (1956) *Nonparametric Statistics for the Behavioral Sciences*. New York: McGraw-Hill.

SPERRY, R (1974) Lateral specialization in the surgically separated hemispheres. In: *The Neurosciences: Third Study Program*. Edited by F. O. Schmitt and F. G. Worden. Cambridge: MIT Press, pp. 5-19.

STEVENS, J. R., MARK, V. H., ERVIN, F., PACHECO, P. and SUEMATSU, K. (1969) Deep temporal lobe stimulation in man: Long latency, long-lasting psychological changes. *Archives of Neurology, Chicago*, **21**, 157-169.

TALAIRACH, J., DAVID, M. and TOURNOUX, P. (1958) *L'Exploration Chirurgicale Stereotaxique du Lobe Temporal dans l'Epilepsie Temporale*. Paris: Masson.

—— —— —— CORREDOR, H. and KVASINA, T. (1957) *Atlas d'Anatomie Stereotaxique*. Paris: Masson.

VALENSTEIN, E. S. (1973) *Brain Control. A Critical Examination of Brain Stimulation and Psychosurgery*. New York· Wiley.

VALENSTEIN, E. S. and NAUTA, W. J. H. (1959) A comparison of the distribution of the fornix system in the rat, guinea pig, cat, and monkey. *Journal of Comparative Neurology*, **113**, 337-364.

VAN BUREN, J. M. (1961) Sensory, motor, and autonomic effects of mesial temporal stimulation in man. *Journal of Neurosurgery*, **18**, 273-288.

—— (1963) The abdominal aura: A study of abdominal sensations occurring in epilepsy and produced by depth stimulation. *Electroencephalography and Clinical Neurophysiology*, **15**, 1-19.

VAN HOESEN, G. W. and PANDYA, D. N. (1975) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. I. Temporal lobe afferents. *Brain Research, Amsterdam*, **95**, 1-24.

—— —— and BUTTERS, N. (1975) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. II. Frontal lobe afferents. *Brain Research, Amsterdam*, **95**, 25-38.

WALKER, A. E. and MARSHALL, C. (1961) Stimulation and depth recording in man. In: *Electrical Stimulation of the Brain*. Edited by D. E. Sheer. Austin: University of Texas Press, pp. 514-518.

WALTER, R. D. (1973) Tactical considerations leading to surgical treatment of limbic epilepsy In: *Epilepsy: Its Phenomena in Man*. Edited by M. A. B. Brazier. New York: Academic Press, pp. 99-119.

WEINGARTEN, S. M., CHERLOW, D. G. and HALGREN, E. (1976) The relationship of hallucinations to the depth structures of the temporal lobe. In: *Neurosurgical Treatment in Psychiatry, Pain and Epilepsy*. Edited by W. H. Sweet, S. Obrador, and J. G. Martin-Rodriguez. Baltimore: University Park Press.

WHITE, L. E., Jr. (1959) Ipsilateral afferents to the hippocampal formation in the albino rat. I. Cingulum projections. *Journal of Comparative Neurology*, **113**, 1-41.

(*Received March 15, 1977*)

Brain (1978), **101**, 119-142

TRIGEMINAL FALSE LOCALIZING SIGNS AND THEIR CAUSATION

by J. E. A. O'CONNELL[1]

(*From the Department of Neurological Surgery, St. Bartholomew's Hospital, London, EC4*)

INTRODUCTION

TRIGEMINAL disturbance occurring in association with unrelated intracranial tumours is a well recognized though not frequent occurrence. The mechanism of its production is not usually apparent, since during surgery for the removal of the neoplasm the affected trigeminal nerve is outside the operative field. In this communication four personally treated patients with such signs are described with details of the radiological investigation and operative findings. Several anatomical observations are discussed: the relatively large size of the tentorial incisura compared with that of the foramen magnum; the relatively small size of the subtentorial as compared with the supratentorial portion of the cranial cavity; the irregularly spherical shape of the posterior fossa; and the anatomy of the trigeminal sensory root, unusual in its course and unique in the change in its direction which occurs at its midpoint as it traverses the foramen of exit from Meckel's cave. On the basis of these observations an explanation for the occurrence of trigeminal false localizing signs is suggested: this may also explain why the signs are associated with extrinsic rather than intrinsic posterior fossa tumours. The mechanism of the widespread paræsthesiæ which may occur in cases of this type is differentiated from that responsible for isolated trigeminal disturbances.

Although a considerable number of valuable accessory methods of investigation are now available for the diagnosis and localization of intracranial masses, the primary approach remains the clinical one. Collier (1904) described false localizing signs in patients with intracranial tumours; that is neurological disturbances arising in structures unrelated to the tumour and therefore not explicable on the basis of compression by it. At the time his paper was a warning to clinicians when, in view of the absence of the diagnostic tests now possible, accurate clinical diagnosis was essential. The subject retains its interest however, since it is not the sign but its interpretation which leads to faulty localization. Compression of structures related to a tumour is not the sole cause of neurological defects in such cases; shifts of the brain may cause clear-cut signs from structures at a distance.

---

[1] Address for reprints: Fishing Cottage, Itchen Abbas, Nr Winchester, Hampshire.

Knowledge of the mechanisms of production of such signs may thus lead to a better understanding of the effects of tumours upon the cranial contents and the remarks which follow are based upon personal experience of a group of patients with trigeminal false localizing signs. In his study, Collier related the clinical and post-mortem findings in 161 cases of intracranial tumour so that inevitably some of the descriptions relate to terminal disease. However, there was much of importance for that period almost three-quarters of a century ago: descriptions of the oculomotor and abducens palsies attributed to posterior shift of the brain, notching of the cerebral peduncles by the tentorial edge and herniation of the cerebellar tonsils into the foramen magnum.

References in the literature to trigeminal false localizing symptoms and signs can perhaps best be separated into two groups—those cases with trigeminal neuralgia and those with other disturbances of the function of the fifth cranial nerve. These will now be considered separately. According to Parker (1928, 1937), the first description of the association of trigeminal neuralgia with a cerebellopontine angle tumour was given by Weisenburg in 1910; he himself described two such cases. In an account of seven years' experience with his posterior fossa approach for trigeminal rhizotomy, Dandy (1932) claimed that lesions responsible for the neuralgia (tumours, aneurysms, etc.) were present in 30 per cent of cases. Hamby (1943) described two personal cases and, indeed, most neurosurgeons will have had personal experience of such cases. Of greater relevance to the present communication and considerably less frequent than the group described above are those cases in which the trigeminal neuralgia is associated with a tumour in the contralateral cerebellopontine angle. The first such case was reported by Bonhoeffer (1915); Parker (1937) described another and Hamby (1947) two more. In the latter three cases it was considered that the trigeminal sensory root was compressed between the brain-stem and either the petrous temporal bone or the free edge of the tentorium. The second group of cases is that in which trigeminal disturbances, other than neuralgia, arise in the presence of an unrelated tumour. Cushing (1917) directed attention to this in his description of acoustic neurinomata. In 9 of 30 patients there was subjective or objective evidence of involvement of the contralateral trigeminal nerve. In another group of 15 patients with subtentorial meningiomata (Cushing and Eisenhardt, 1938) two had well-marked contralateral trigeminal symptoms and signs. He states that similar cases had been recorded by Funkenstein (1905) and by Bonhoeffer (1915). In considering the explanations which had been put forward for the various contralateral symptoms and signs Cushing felt that none of them was entirely satisfactory. He points out, however, that in the case of the trigeminal nerve there 'must be a sharp angulation of the root at its point of entry into its tentorial foramen'. D'Errico (1950) described 10 cases of meningioma of the cerebellar fossa; 6 of these had trigeminal sensory reduction, ipsilateral to the tumour in 3 and contralateral in 3. Castellano and Ruggiero (1953) analysed a series of 71 cases of posterior fossa meningioma of which 7 were placed over the cerebellar convexity; of the 5 with trigeminal disturbance this was contralateral in 2, ipsilateral in one and bilateral in 2. These symptoms were considered to be due to pressure by the tumour through the cerebellum on the trigeminal root or roots. Paillas, Pellet, Janny, Tournilhac and Komminoth (1969) described 7 personal cases in which contralateral cranial nerve disturbance arose in the presence of posterior fossa neoplasms; in 6 of these, the trigeminal nerve was involved. They review the literature and mention that Wernicke had suggested that the root might be subject to pressure on the sharp edge of the dural foramen through which it emerges into the posterior fossa. The authors conducted experiments in the cadaver with artificial tumours. They point out that the trigeminal defect occurs only in the presence of tumours of large size and firm consistency and that the resulting displacement of the brain-stem is of prime importance in occasioning the cranial nerve disturbance. They conclude with the statement that an eclectic attitude is best in approaching this problem, more important being an awareness of the occurrence of contralateral cranial nerve involvement in the presence of posterior fossa tumours. Northfield (1973) suggested that trigeminal pain and sensory reduction in the presence of unrelated tumours may be occasioned by brain penetration through a deficiency in the dura mater covering the semilunar ganglion or a herniation of cerebellum into Meckel's cave.

Direct observation of the trigeminal nerve affected in patients with these false localizing signs will rarely be possible. Where the signs are contralateral to the tumour the affected nerve will not be exposed at all; where ipsilateral, the approach being a sub-occipital one, the nerve will not be exposed until the tumour has been excized and distortions which it had occasioned have been corrected. Therefore an explanation of these signs must be based on indirect evidence. That to be suggested in this paper is based on clinical experience of a group of patients with trigeminal false localizing disturbances and some anatomical observations. It is hoped that the review of the relevant literature and the personal observations reported may be a contribution towards the elucidation of the problem of the mechanism of the production of the signs.

CASE REPORTS

The records of a personal group of patients with trigeminal disturbance of false localizing portent will now be considered. Although detailed radiological reports were available in all cases destruction of some of the films makes their reproduction impossible

Case 1 G. S., a 42-year-old male clerk was first seen in 1954, complaining that for six months he had had left tinnitus and distortion of telephoned voices in his left ear. Hearing then deteriorated and some rotational vertigo developed. There were no other symptoms and on neurological examination the sole abnormality was that of the left eighth cranial nerve, there being a very marked hearing loss and an absent caloric response. Skull films showed enlargement of the internal auditory meatus on the left and a diagnosis of a left-sided acoustic neurinoma was made. As the patient did not wish operation and, indeed, it was not considered indicated at the time, he was followed regularly in the outpatient department. After some years he reported occasional recurring paræsthesiæ over the left side of the face and examination showed slight sensory reduction on this side with a reduced corneal reflex. At this time there was also a transient slight left facial paresis and nystagmus to the left. In 1960 he began to have occasional shooting pains in the right face. By 1964 he had clearcut right-sided trigeminal neuralgia involving the second and third divisions. He was treated with carbamazepine and responded well. Later, when some mild left ataxia appeared, the wisdom of admission for investigation and excision of his tumour was raised but the patient still did not wish this. By 1970 his trigeminal neuralgia ceased to be controlled by drug therapy and he requested treatment for this but not for his tumour. A section of the right trigeminal sensory root was carried out by the temporal approach. His pain was relieved and when last seen in 1976 he remained well, apart from the left tinnitus and deafness. Skull films made at intervals over the years have revealed increased erosion of the left internal auditory meatus.

It is very probable that the tumour in this patient's left cerebellopontine angle is a slowly growing acoustic neurinoma producing no symptoms of raised intracranial pressure and having as its essential manifestation involvement of the left eighth nerve. It seemed likely that the right-sided trigeminal neuralgia was occasioned by this left angle tumour but the mechanism of the involvement was not clear.

Case 2. J.S., a 45-year-old male factory worker was admitted in 1963, complaining of headache and numbness of the right side of his face. Two years previously he developed frontal headache, at first intermittent and worse in the mornings. It became constant and increasingly severe and vomiting soon appeared, also usually in the morning. After a year of these symptoms, numbness of the right face developed and persisted. Two months before admission severe vertigo developed and unsteadiness of gait appeared. This, too, was worse in the morning and occasioned many falls. Examination revealed bilateral papillœdema with hæmorrhages on the right. There was a horizontal nystagmus, coarser on looking to the left, and sensation was reduced in the right trigeminal field. Audiometry and labyrinthine tests were normal. The tendon reflexes were brisk and the plantar responses extensor. There was truncal ataxia with a tendency to fall backwards. Skull films showed rarefaction of the sellar cortex and an erosion of the right occipital squama. Ventriculography revealed an internal hydrocephalus involving the lateral and third ventricles; the aqueduct was wide and kinked and slightly displaced to the left; the fourth ventricle was similarly displaced. A right-sided sub-occipital approach was made and beneath the bone a layer of extradural tumour was uncovered. A spherical fibroblastic meningioma, 4 to 5 cm in diameter and attached to the dura mater a short distance below the lateral sinus was excized. After removal of the tumour the right cerebellopontine angle was carefully explored and the trigeminal sensory root appeared entirely normal. The patient made a complete recovery and has remained well.

The mechanism of production of the ipsilateral subjective and objective right trigeminal sensory disturbance was not clear.

Case 3. B. W-S., an unemployed, 49-year-old spinster, was first seen in 1960 with a number of complaints. She had been in poor health for four years, complaining of loss of appetite, nausea, headache and attacks of dizziness with weakness of the legs, occasioning numerous falls. She had had treatment for depression. After three years numbness, followed by aching pain, developed in the left face. Her condition deteriorated and she showed early dementia. The finding of papillœdema led to her being referred for investigation. Examination revealed an anxious, rational woman whose fundi showed high bilateral papillœdema with hæmorrhages, consecutive optic atrophy and greatly reduced visual acuity. There was a horizontal nystagmus to both sides and reduction of all forms of sensibility in the left trigeminal area. The lower limb tendon reflexes were brisk and the plantar responses probably extensor. The gait was unsteady but Romberg's sign was negative. Skull films showed decalcification of the posterior clinoid processes and ventriculography (fig. 1A and B) an internal hydrocephalus with displacement of the aqueduct forwards and to the left, as also of the fourth ventricle which was slightly elevated. A right-sided sub-occipital exposure was made and marked dural tension revealed. A firm tumour was exposed and its centre quickly removed to reduce tension: histological examination showed it to be a fibroblastic meningioma. The large globular mass was separated from the cerebellum inferiorly and laterally. Superiorly it was in contact with, but not attached to, the tentorium cerebelli. Medially it had an extensive attachment to the falx cerebelli which it had perforated to embed itself in the medial

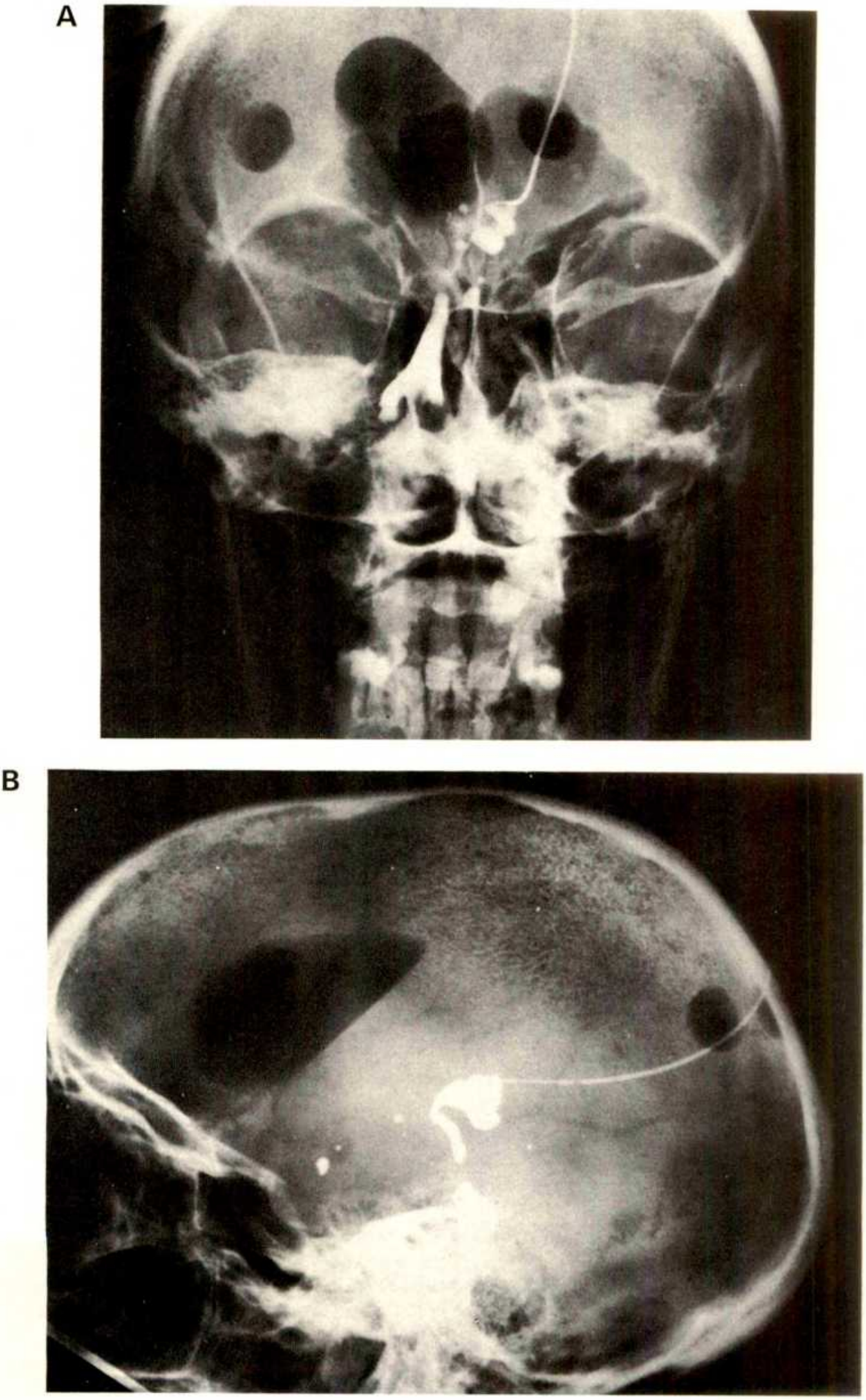


FIG. 1. *Case 3.* A and B, myodil ventriculogram.

portion of the left cerebellar hemisphere. Superiorly it was attached in the angle between the tentorium and the dura mater over the cerebellum. Total excision was effected and the area of attachment cauterized. Post-operative progress was good although vision remained severely impaired. Three years later there was a considerable general improvement including that of the vision in one eye. The patient still complained of slight pain in the left side of the face and sensation remained reduced in the second and third division territory of this side.

The mechanism of production of the contralateral trigeminal disturbance in this case was not clear and it is noteworthy that it persisted, though diminished, following removal of the growth, although the patient was much improved in all other respects.

Case 4. R. D-B., a 33-year-old housewife, was first seen in 1964. She had been well apart from two transient attacks of loss of consciousness twelve and five months prior to the development of the symptoms which caused her to be referred; the attacks had been regarded as syncopal. She considered that her illness commenced nine months before she came to hospital with attacks of long-lasting frontal headache occurring once or twice a week. These slowly worsened and attacks of paræsthesiæ in both hands appeared and would last for fifteen minutes. She was temporarily improved by a period of rest and then had an agonizingly severe attack of headache with nausea and unformed visual hallucinations lasting for almost a week. Her legs became weak and stiff at this time. Three months before admission she developed constant numbness in the face on both sides, the cheeks being particularly affected, and was troubled by a roaring bilateral tinnitus. The symptoms continued and worsened and there were added to the headache, neck stiffness, persistent stiffness and weakness of the legs and again intermittent paræsthesiæ in the hands. Examination revealed a somewhat euphoric woman, slow in her responses and performing simple intellectual tests poorly. There was neck stiffness and diffuse skull tenderness. Papillœdema was marked and there was a right homonymous hemianopia, the pupil reactions being sluggish. Sensory reduction was present in the territory of the second division of the trigeminal nerve bilaterally. There was no other disturbance of motor or sensory function. The tendon reflexes were brisk but the cutaneous ones normal. Her gait was shuffling with deviation to the right. The skull films showed pressure abnormalities in the sella turcica and displacement anteriorly and inferiorly of its dorsum (fig. 2A). Ventriculography and carotid angiography showed evidence of a very large mass in the posterior portion of the left cerebrum. Midline structures including the falx, especially posteriorly, were displaced to the right (fig. 2B, C, D and E). The posterior end of the third ventricle was squeezed and the fourth ventricle also displaced to the right. At craniotomy an extremely large meningioma was found attached to the lateral sinus from a point immediately to the left of the falx for a distance of some 3 cm. It extended forward on the tentorium to the superior surface of the petrous temporal bone and had a wide area of contact with the falx cerebri, deeply excavating the temporal, occipital and deep parietal lobes. A total excision was effected and the area of the attachment to the lateral sinus was cauterized. Histological examination revealed a fibroblastic meningioma. No explanation for the bilateral trigeminal sensory reduction was seen. The patient made an excellent recovery but eight years post-operatively developed various symptoms which led to investigation to exclude the possibility of a posterior fossa extension of the original mass. This possibility was excluded and the symptoms cleared up.

Case 5. D.M., a 39-year-old-salesman, was admitted in 1964 complaining of headache. Nine months previously he first noticed severe but transient sub-occipital headache on straining. Subsequently this would recur on bending and straining. After three months pain recurred each morning, aggravated by bending and easing later in the day; it was associated with well-marked neck stiffness. With the passage of a further three months attacks of severe headache were more frequent. One month before admission headache became agonizing and with this he would have paræsthesiæ in his face and arms. Attacks of blurred vision, lasting for thirty minutes, developed. Finally, he felt unsteady on his feet and, during an attack of headache, paræsthesiæ spreading from the face to the arms and legs occurred and there was associated weakness of the legs; at the same time he was dyspnœic. Examination revealed neck stiffness and bilateral papillœdema with hæmorrhages. External ocular movements were full without nystagmus and it was possible that there was a slight right facial weakness. There were no other abnormal signs,

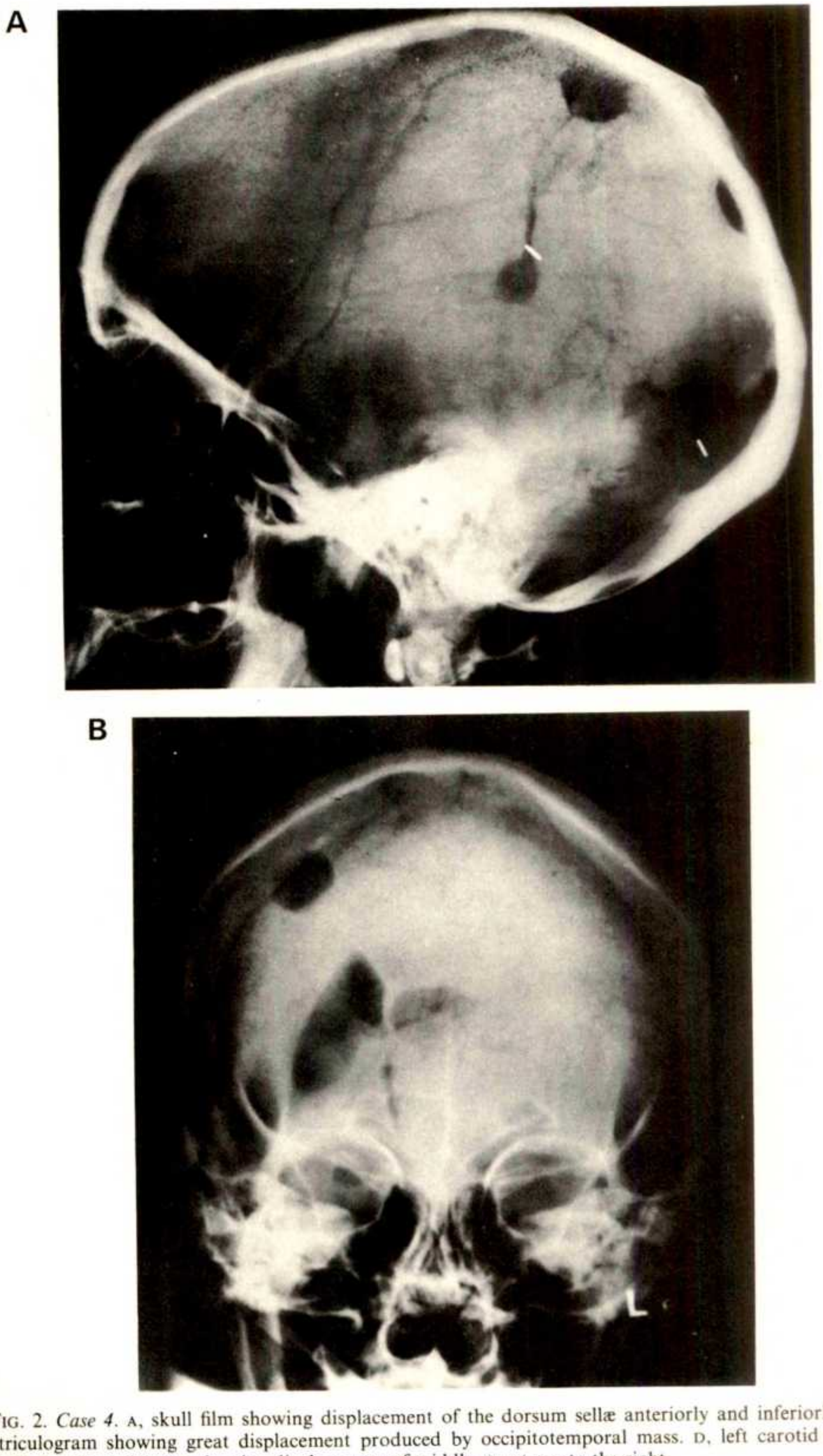
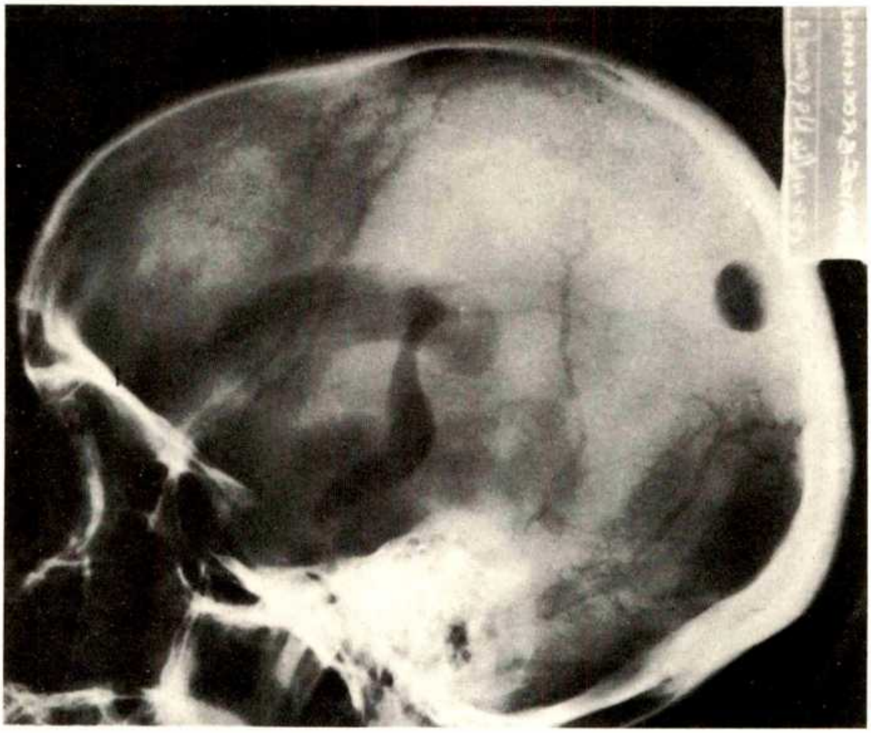
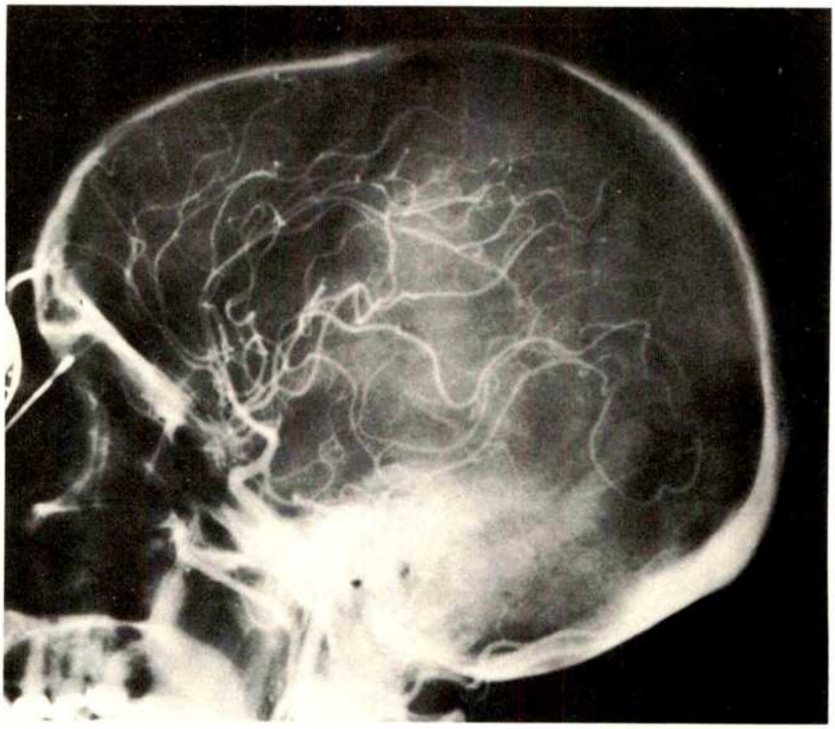


FIG. 2. *Case 4*. A, skull film showing displacement of the dorsum sellæ anteriorly and inferiorly. B and C, ventriculogram showing great displacement produced by occipitotemporal mass. D, left carotid angiogram. E, right carotid angiogram showing displacement of middle structures to the right.

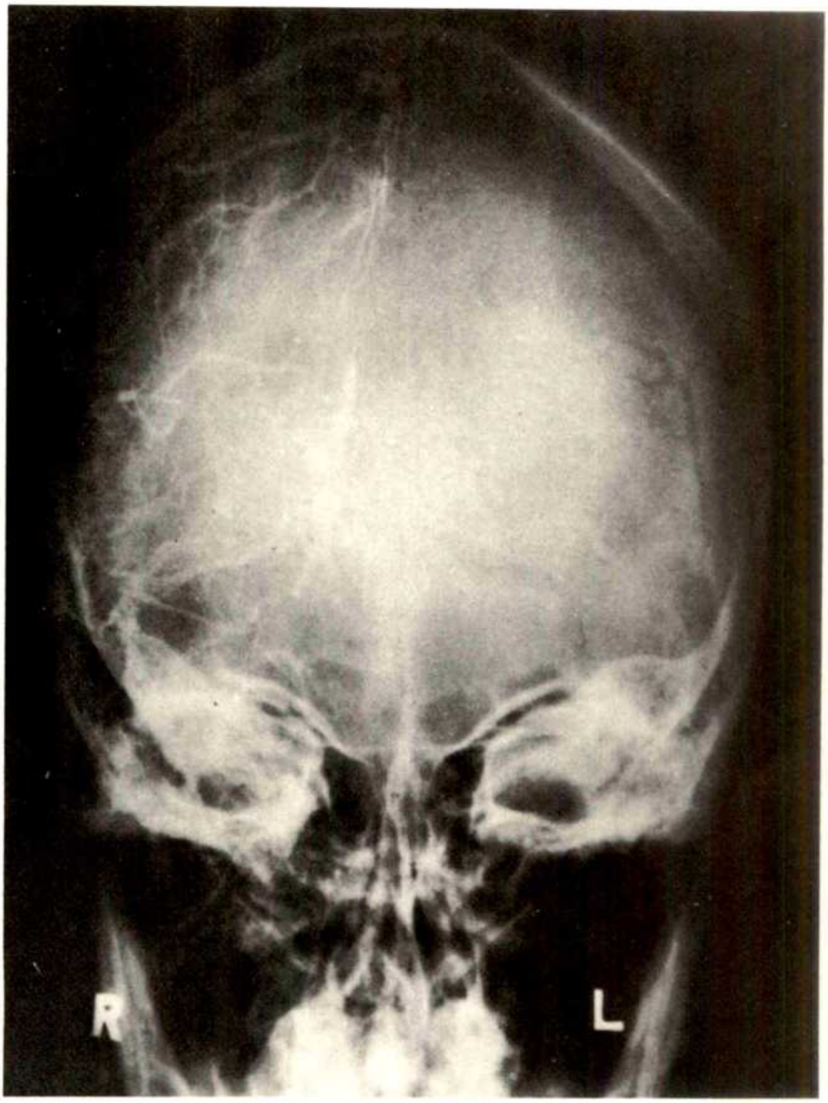
C



D



E



station and gait being normal. Skull films showed thinning of the sellar floor and ventriculography an internal hydrocephalus with the aqueduct flattened and displaced forward and to the right, the fourth ventricle being similarly displaced. Exploration by means of a left unilateral sub-occipital approach was made. In the base of the left cerebellar tonsil (which had herniated into the foramen magnum) a red tumour mass, 2·5 cm in diameter, was seen beneath the arachnoid. After tapping the left lateral ventricle and the cisterna magna to reduce the high pressure, the mass was excized from a markedly œdematous left cerebellar hemisphere. No cyst was present, the tumour was a solid hæmangioblastoma. He made an excellent recovery and has remained well.

To summarize this clinical experience, 4 patients experienced subjective and/or objective trigeminal disturbance contralateral to the neoplasm in 2, ipsilateral in one and bilateral in one. Two patients, including one of those just mentioned, experienced transient attacks of neck stiffness with widespread paræsthesiæ and weakness of the lower limbs. Clearly the cases with persisting trigeminal disturbance must be differentiated from those in which the paræsthesiæ are not only transient but widely distributed.

ANATOMICAL OBSERVATIONS

The localizing symptoms and signs of an intracranial neoplasm result from the close anatomical relationship between the nervous structures involved and the mass. False localizing signs must also have an anatomical basis though not an immediately obvious one. In this belief a number of anatomical observations have been made in an attempt to explain the mechanism of trigeminal false localizing signs.

(1) *The Volume of the Posterior Cranial Fossa*

In addition to the brain, the skull contains the cranial meninges, and volumes of blood and cerebrospinal fluid, both of which fluctuate; the latter volumes vary, in part reciprocally. The average weight of the brain in the adult is 1450 g in the male and 1350 g in the female (*Gray's Anatomy*, 1973) and it attains its adult volume at the age of 17 years. The cranium develops as a capsule for the brain, grows with it and ceases to grow when brain volume has attained its maximum. Cranial volume will obviously vary with brain volume and it is therefore believed that measurement of the volume of the portions of the brain above and below the tentorium will provide an indication of the volume of the supra- and infratentorial portions of the cranium, at least in so far as their relative size is concerned.

Such measurements were made in four cadavers (Table 1). They indicate that the volume of the posterior cranial fossa is 12 per cent of that of the total intracranial volume and 14 per cent of the supratentorial volume. These figures raise

TABLE 1. WEIGHTS AND VOLUMES OF SUPRA- AND INFRATENTORIAL PORTIONS OF THE BRAIN

	Brain 1	*Brain 2*	*Brain 3*	*Brain 4*	
Age and sex	*M.63*	*F.86*	*F.63*	*F.70*	*Mean*±*SD*
Supratentorial brain					
Weight (g)	1352	1200	1146	1050	1187±126·3
Volume (cc)	1275	1132	1081	991	1120±118·8
Infratentorial brain					
Weight (g)	176	176	168	134	163·5±20·02
Volume (cc)	166	166	158	126	154±19·04

Brain volumes calculated from weight after determination of specific gravity in Brain No. 2 (Sp.G. = 1·06).

the problem of how a posterior fossa neurinoma or meningioma with a volume of one-fifth or more of that of the fossa can be accommodated as readily as a similar or even smaller tumour in the supratentorial compartment. Such mechanisms of compensation such as decrease in the amount of intracranial blood, diminution of the tissue fluid in the brain related to the mass, and displacement of cerebrospinal fluid might be expected to be as efficient above as below the tentorium. Possibly, therefore, brain displacement has particular importance in the presence of posterior fossa masses.

(2) *The Relative Sizes of the Tentorial Incisura and the Foramen Magnum*

The antero-posterior and transverse diameters of these two foramina were measured in four cadavers (Table 2). The area of each foramen was then measured by means of drawings on graph paper. These revealed that the area of the foramen magnum was 20 per cent of that of the tentorial incisura. It must, of course, be realized that variations in the shape and size of these foramina occur. For example, in the case of the tentorial incisura, Sunderland (1957) gave variations of the antero-posterior measurement of 44 to 75 mm and of the transverse measurement of 19 to 35 mm; some relationship appears to exist between these variations and the antero-posterior and transverse measurements of the cranium. Whatever the variations, however, it is clear that the tentorial incisura is a very much larger defect in the boundaries of the posterior fossa than is the foramen magnum. Much attention has been directed towards herniations of the cerebellar tonsils into the foramen magnum, no doubt partly due to the dangers of inducing medullary compression by lumbar puncture in the presence of such a pressure cone. Another reason may be the fact that a foraminal pressure cone is clearly seen during surgical explorations. In addition it might appear that the downward herniation of posterior fossa contents would be in part a gravitational effect. However, it must be recalled that the comparative densities of nervous tissues and cerebrospinal fluid are such that a brain and spinal cord which weigh 1,500 g when removed from the craniospinal space have an *in situ* weight of only 50 g (Ruch and Patton, 1965). Thus, bearing in mind the relative sizes of the foramina, herniations into the larger tentorial opening are likely to be more frequent than those into the foramen magnum. It is also of importance that an interval exists between the upper margin of the pons

TABLE 2. DIMENSIONS OF TENTORIAL INCISURA AND FORAMEN MAGNUM

	Cranium 1	*Cranium 2*	*Cranium 3*	*Cranium 4*	
Age and sex	*M.63*	*F.86*	*F.63*	*F.70*	*Mean ± SD*
Tentorial incisura					
AP (mm)	54	62·5	55	51·5	55·75±4·73
Transverse (mm)	30·5	30·5	24	29	28·5±3·08
Foramen magnum					
AP (mm)	15	14·5	17	17	15·9±1·31
Transverse (mm)	22	23	24	23	23·0±0·82

and the dorsum sellæ. This varies from 2 to 12 mm, averaging 6 mm in the cadaver (Sunderland, 1957); thus the pons can move anteriorly in relation to the incisura as well as superiorly and to either side. Perhaps displacements of the brain towards and into the foramen may supply an answer to the problem raised in the previous section and provide accommodation for posterior fossa tumours of greater size than might be thought possible.

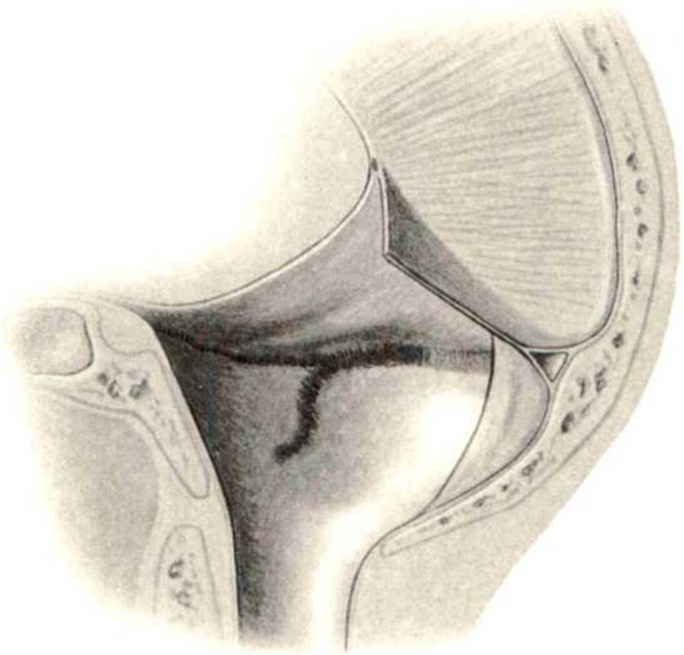


FIG. 3. Drawing of posterior fossa in section indicating direction of dural surfaces constituting its roof.

(3) *The Shape and Boundaries of the Posterior Fossa*

In shape, the posterior fossa is an irregular sphere (figs. 3 and 4). The superior hemisphere or roof contains anteriorly the large obliquely placed tentorial incisura with its base at the dorsum sellæ and its apex at the point of attachment of the tentorium to the falx cerebri. On each side of this the tentorium slopes downwards and outwards to its circumferential cranial attachment; its inferior surface on each side is directed not only inferiorly but also anteriorly and medially (fig. 3). The inferior hemisphere or floor of the fossa contains the foramen magnum in the mid-line anteriorly; from the posterior half of the circumference of this foramen the cranium passes posteriorly and laterally with but a slight upward tilt to meet the line of attachment of the tentorium along the lateral sinus (fig. 4). This floor is formed by the cerebellar fossæ which are, therefore, directed largely superiorly and there is but little which can be regarded as a true posterior wall of the fossa. The

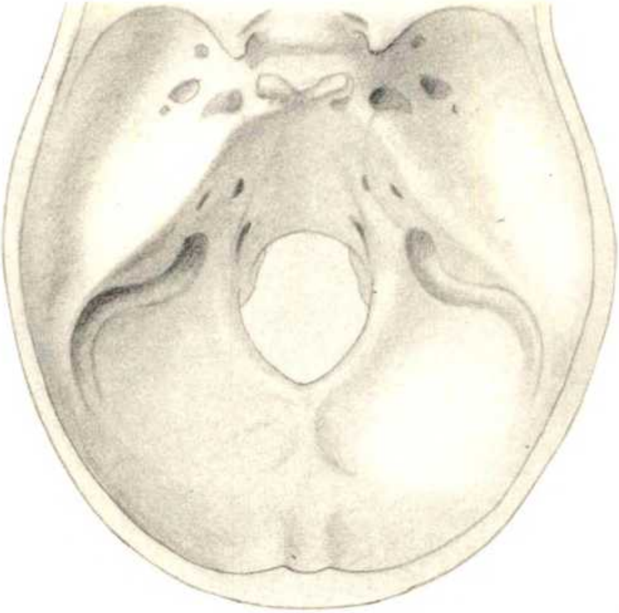
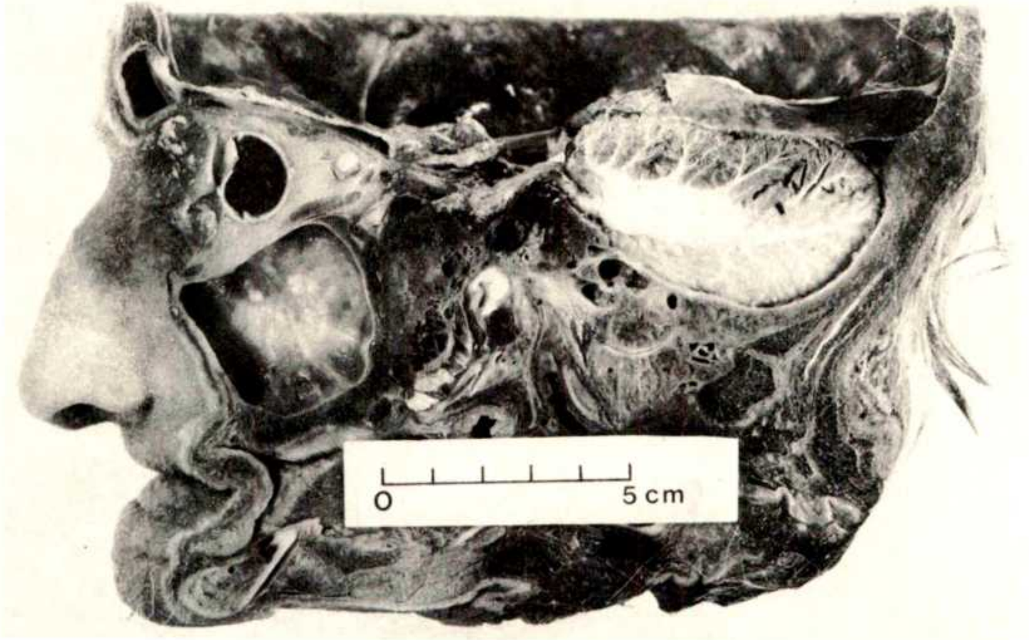


FIG. 4. Drawing indicating direction of the bony surfaces constituting the inferior hemisphere of the posterior fossa.

floor of the fossa anterior to the foramen magnum in the midline is formed by the clivus, whose sloping surface faces posteriorly and superiorly. On each side is the posterior surface of the petrous temporal bone; the obliquely directed superior margin of the petrous bone gives attachment to the tentorium and its surface in the posterior fossa is directed posteriorly and medially with but a slight upward inclination. The lateral wall of the fossa is a small area posterior to the sigmoid sinus directed medially and anteriorly. As will be seen, it is considered that these anatomical features all contribute to displacement of the contents of the posterior fossa into the supratentorial area in the presence of tumours arising from the floor of the fossa. Tumours arising from the antero-lateral wall of the fossa will be seen to occasion a different displacement.

(4) *Some Features of the Anatomy of the Trigeminal Sensory Root*

The sensory root of the semilunar ganglion is the largest such root of a cranial nerve and 20 to 25 mm in length. From the viewpoint of its anatomical relationships it can be considered to have two segments of equal length. The first portion extends posteriorly and superiorly from the semilunar ganglion to the dural foramen through which it enters the posterior fossa. It lies, with the posterior portion of the ganglion beneath two layers of dura mater in the subarachnoid space



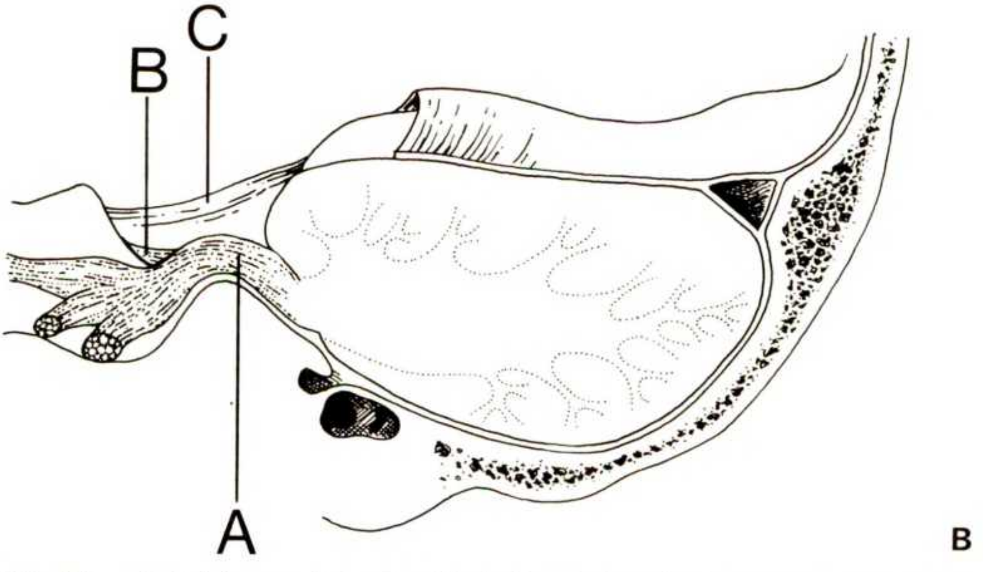


FIG. 5A, photograph of a left parasagittal section of the head passing immediately lateral to the left semilunar ganglion and its sensory root. B, sketch of photograph. A, left sensory root; B, right sensory root; C, right free margin of tentorial.

of Meckel's cave, isolated from the general intracranial cavity. The second portion crosses the posterior fossa to its pontine attachment at the junction of the superior and middle thirds of the anterior surface of that structure. Its direction is a posterior and inferior one and it lies below and slightly lateral to the free tentorial edge. In the cadaver (figs. 5A and B) the two portions of the root meet at an angle which may be as small as 90 degrees; however it is likely that during life this change in direction will be less marked since the cerebellum and pons will be elevated by cerebrospinal fluid floatation lacking in the cadaver. Unlike the anterior portion of the root, that within the posterior fossa is fully exposed to compression by related posterior fossa masses and to distortion occasioned by brain-stem displacement. It is thought that at the point of change in the direction of the sensory root, injury arising from traction forces may be occasioned by the margins of the dural foramen through which it passes.

DISCUSSION

The suggestion that a general rise in pressure resulting from a neoplasm in the posterior fossa can explain trigeminal false localizing signs is inadequate. The most common of the posterior fossa cranial nerve disturbances occasioned by unrelated tumours is that of the abducens. This was at one time regarded as due to compression of the nerve during its long intradural course (Uhthoff, 1906). However, this palsy is now considered to be due either to traction on the nerve from brain-stem displacement or vascular constriction by branches of the basilar artery when the brain-stem is enlarged by neoplasms within it (Cushing, 1910). Excluding the abducens, of the other seven cranial nerves on each side of the posterior cranial fossa the trigeminal is possibly the most commonly and frequently the only one affected and this dysfunction may be unilateral or bilateral. A rise in pressure in the posterior fossa will be equally distributed through the space and cannot explain these facts.

At the tentorial incisura and the foramen magnum increased intracranial pressure produces effects not seen in other parts of the cranial cavity displacing brain tissue into one or both defects as a decompressive phenomenon; nervous structures related to these openings may be involved in such displacements. Thus in the case of a downward transtentorial pressure cone the displacement inferiorly of temporal lobe and midbrain occasions stretching and compression of the occulomotor nerve which crosses the incisura anteriorly. The clinical picture which results was once regarded as being due to raised intracranial pressure but is now well-known to be the result of brain displacement at the tentorial opening with brain-stem and occulomotor nerve compression. At the foramen magnum the displacement inferiorly of cerebellum and medulla gives rise to compression of the medulla with involvement of the long motor and sensory tracts and later respiratory failure in the conscious patient. It is thought that the displacement of nervous tissues into the tentorial opening from below can in the same way produce brain-stem and cranial nerve compression; in this case the trigeminal nerve, in view of its close relationship to the incisura, is that most exposed to injury.

As a neoplasm grows in the posterior cranial fossa a stage is reached when displacement of the contents of the fossa must occur. When the tumour lies on the floor of the fossa the factors already described will lead to a displacement of the related portion of the cerebellum superiorly, anteriorly and medially towards, into, and eventually through the tentorial incisura. The cerebellar peduncles will involve the brain-stem in this displacement. Some degree of mobility of the brain-stem in its long axis is to be expected, bearing in mind the floatation of the brain within the cranium and the need for sufficient slack in the neuraxis at the cranio-spinal junction when the head and neck pass from a position of full extension to one of full flexion (O'Connell, 1956). Moreover, as has been seen, downward displacement of the brain-stem occurs as part of the pressure cone secondary to supratentorial masses. Collier (1904) explained the paralysis of the abducens nerve in cases of increased supratentorial pressure as being the result of a posterior shift of the brain-stem and stretching of this nerve in its vertical course in a direction opposite to that of the brain displacement. Cushing (1910) was not entirely satisfied with this explanation. He noted that the abducens nerves were crossed on their superficial aspect by transversely-directed branches of the basilar artery and that when the pons and medulla were enlarged by tumours or œdema the vessels grooved to a varying extent the brain-stem and these nerves. When the responsible lesion is supratentorial, however, such brain-stem swelling is absent and Collier's hypothesis of traction injury appears to provide the best solution of the ætiological problem.

Upward movement of the brain-stem is also a recognized occurrence in the presence of a posterior fossa mass. Clinical evidence of it was noted, though not explained, by Cushing and Eisenhardt (1938) in cases of posterior fossa meningiomata—a loss of superficial reflexes and exaggerated deep ones. Knupling and Fuchs (1975) in similar cases found unilateral or bilateral hyperreflexia more marked in the lower limbs. They also found pathological changes of degenerative type in the cerebral peduncles and considered that the findings resulted from an ascending transtentorial herniation and compression of one or both cerebral peduncles against the clivus or tentorial edge. These authors mention that in a group of 11 patients with posterior fossa meningiomata and such signs of brain-stem compression, only 6 survived investigation and treatment. While the 3 personal cases with meningiomata producing trigeminal false localizing signs recovered well, they were all ill pre-operatively with evidence of long-standing high intracranial pressure. Radiologically, such ascending pressure cones displacing and deforming the posterior portion of the third ventricle are well recognized (Le Beau, 1944; Ecker, 1948) and not uncommon. Indeed, in the absence of such a gross radiological change the kinking of the sylvian aqueduct frequently demonstrated in cases of posterior fossa neoplasm (Lysholm, 1939; Twining, 1939) implies an upward displacement of the brain-stem, the anterior displacement of the pons and medulla being associated in addition with upward movement on the steeply sloping surface of the clivus.

To consider first the group of patients in whom the neoplasm, while unrelated to the affected nerve, is in direct contact with the brain-stem. Here false localizing trigeminal disturbance is associated with tumours of the contralateral cerebellopontine angle (fig. 6). A tumour in this situation lies lateral to the brain-stem and anterior and inferior to the cerebellum. As the tumour enlarges the brain-stem will be displaced to the opposite side and the cerebellum displaced posteriorly and superiorly. Some rotation of the brain-stem will occur so that its ventral surface is turned towards the tumour. The horizontally-directed nerves on the side of the tumour (seventh, eighth, ninth, tenth and eleventh) will be stretched both around the growth and as a result of the brain-stem displacement; in the course of time defects of their function result. These nerves on the contralateral side will be relaxed by the displacement. The anteriorly-directed fifth nerve on the side of the

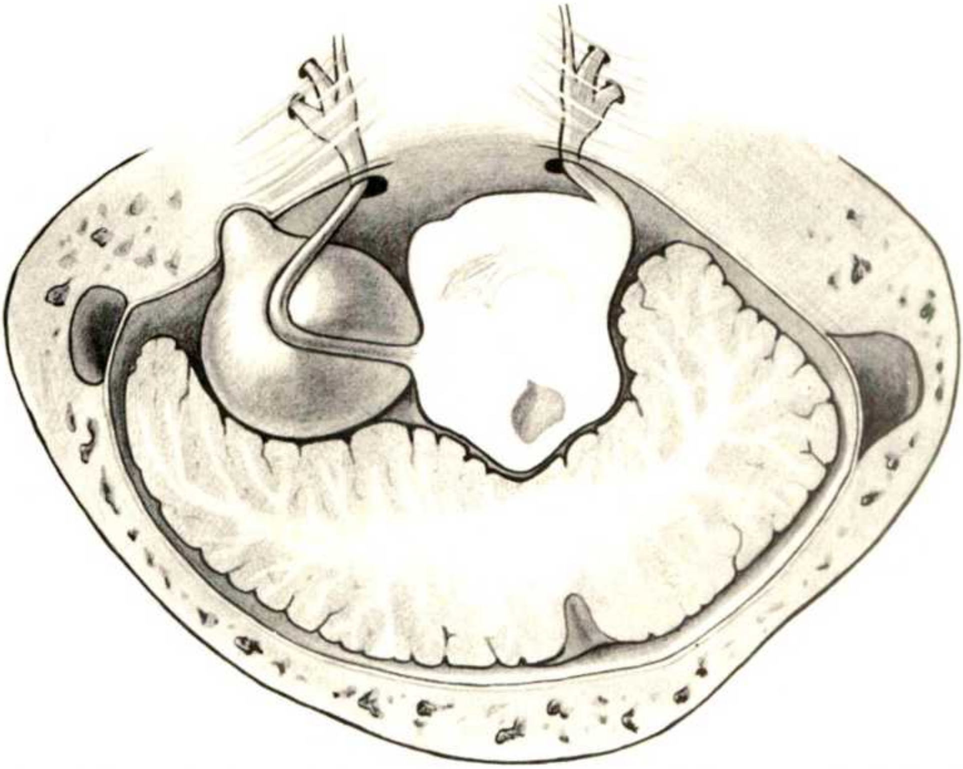


FIG. 6. Schematic drawing indicating the distortion of the trigeminal sensory root secondary to brain-stem displacement from a contralateral tumour of the cerebellopontine angle.

tumour will be stretched over the mass resulting in the varying degrees of dysfunction typical in such cases. On the contralateral side the anteriorly-directed trigeminal sensory root, unlike the nerves that pass laterally, will be rendered tense by the brain-stem displacement. It will be stretched around the lateral margin of the dural foramen, through which it leaves Meckel's cave, and compressed by it. In this manner, trigeminal disturbance, such as pain, paræsthesiæ or a sensory defect on the side opposite to an angle tumour may be explained.

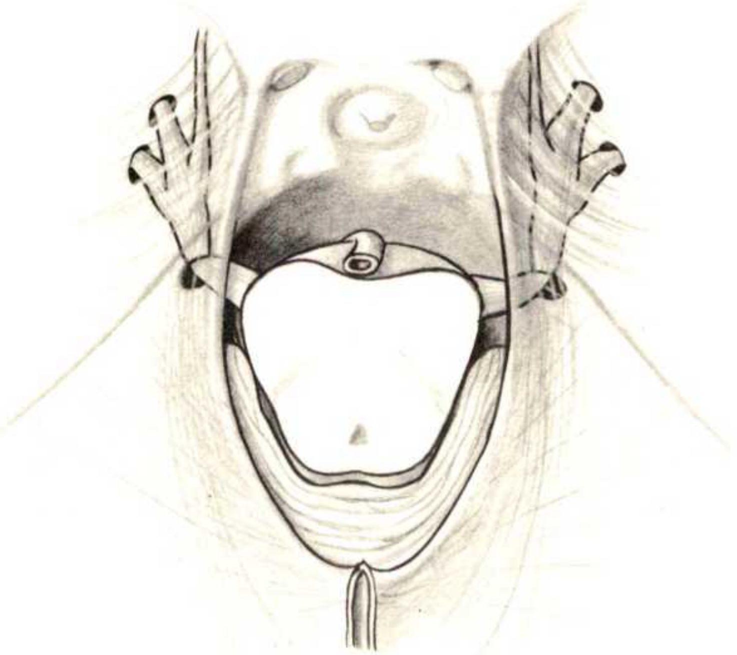


FIG. 7. Schematic drawing indicating the distortion of the trigeminal sensory root secondary to brain-stem displacement caused by a meningioma of the cerebellar fossa.

Turning to the group of patients with meningiomata of the cerebellar fossa, these may occasion considerable displacement of the brain-stem to the opposite side. Contralateral trigeminal symptoms can thus be explained in the same way as those due to cerebellopontine angle growths as described above, but where the trigeminal disturbance is ipsilateral or bilateral another explanation must be sought. Although, as seen during surgical exploration of the posterior fossa, these tumours may appear to be posterior to the cerebellum, they are, in fact, largely inferior to it. As the tumour enlarges, the cerebellum will be displaced superiorly and anteriorly, the latter element of the displacement being maintained by the inferior surface of the tentorium. The medial direction of the tentorial surface and that of the posterior surface of the petrous temporal bone will add a medial element to this brain displacement while the sloping surface of the clivus will contribute to both the superior and anterior elements of the movement. The displacement of cerebellum and brain-stem is thus an antero-superior and slightly medial one. The attachment of the trigeminal sensory root to the pons will, of course, be carried in these directions. It is believed that this displacement of the central attachment of the sensory root will exert traction upon it, and that this will occasion injury to it at the point of its sharp angulation at the foramen through which it enters the posterior fossa from Meckel's cave. When the brain-stem displacement is marked the sensory root may also be compressed against the free margin of the tentorium. In the presence of a tumour of the cerebellar fossa displacement of the brain-stem to the side opposite to the tumour, or superiorly, or a combination of the two displacements, gives rise to trigeminal false localizing signs; variations in the degree of the two displacements can explain why the signs may be ipsilateral, contralateral or bilateral. It is likely that such anatomical variations, such as the size of the tentorial incisura and the directions of the various dural and bony surfaces enclosing the posterior fossa, will increase or decrease the possibility of such signs developing.

In the case of the supratentorial tumour (Case 4) no explanation for trigeminal disturbance at first suggested itself. However, following the study of cases of this disturbance with posterior fossa tumours, it appeared that the explanation might be a similar one based on brain-stem displacement. In this particular patient the very large meningioma spread from the falx medially to the convexity of the cerebral hemisphere laterally, and it extended from the occipital pole to the superior surface of the petrous temporal bone. The left posterior cerebrum was thus lifted completely from its normal position in the recess between the sloping superior tentorial surface and the cranium. Plain skull films showed that the dorsum sellæ was displaced anteriorly and inferiorly by the brain-stem (fig. 2A). This film was made eight years after operative treatment when the patient was re-investigated for headache and the possibility of a subtentorial extension of the original growth was excluded. However, the same sellar displacement was present in the original films but re-calcification of the dorsum makes the displacement more easily visible in the later ones. The features of the pre-operative ventriculogram relevant to the present discussion were those of a massive left-sided tumour (figs. 2B and C) which occasioned narrowing and displacement to the right of the posterior portion of the third ventricle as well as a similar displacement of the fourth ventricle. The right carotid angiogram (fig. 2C) showed a marked displacement of midline structures to the right; this was so great as to suggest that either the falx itself was displaced or else that it had been perforated by growth; since there was no evidence of such penetration at operation, marked displacement of the brain-stem to the right had occurred. In addition, the large tumour had occasioned anterior displacement of the brain-stem. This brain-stem displacement, anteriorly and to the right side, produced by a supratentorial mass would almost certainly be associated with a movement of it superiorly relative to the tentorial incisura; the structure would be drawn superiorly instead of being pushed in this direction as in the previously described cases. It is thought that the trigeminal disturbances in this case were occasioned by the stretching of the two trigeminal sensory roots (as a result of brain-stem displacement) and trauma to them at the point of the angulation of each at the dural foramen of exit from Meckel's cave, and possibly also around the tentorial edge.

It will be noted that the area of the trigeminal territory affected varied: thus in the patient (Case 4) with the supratentorial meningioma, the numbness and hypoalgesia involved the maxillary divisions of both sides. In Case 3 both disturbances were contralateral and involved the maxillary and mandibular divisions. In Case 2 the disturbance was ipsilateral and all three divisions of the nerve were involved. The only explanation which can be suggested is variations in the brain-stem displacement and the resulting deformation of the trigeminal sensory root or roots.

As has been seen (Paillas *et al.*, 1969), the responsible tumour in cases with trigeminal false localizing signs is usually of large size and firm consistency. From a study of the literature it appears that as in the cases here reported, the tumours responsible for these signs are usually extrinsic (meningiomata, neurinoma, etc.) and not intrinsic (gliomata, hæmangioblastomata). This is unexpected when it is recalled that the latter type of tumour when cystic may be of great volume and considerably larger than most meningiomata or neurinomata. How can this be explained? An extrinsic tumour in the posterior fossa will from its earliest development displace the related portion of cerebellum or brain-stem. The direction of the displacement will be determined by the direction of the bony surface beneath the base of the mass. This process will continue but the movement of more distant portions of the cerebellum and brain-stem will be governed by the directions of the bony and dural surfaces with which they come in contact. In the case of a cystic cerebellar tumour the pressure rises within the cerebellum and will expand it equally in all directions. While great general displacements may eventually result, the directional displacement seen with extrinsic tumours from the beginning of their development will not occur.

Involvement of cranial nerves unrelated to an intracranial tumour is of course not confined to the trigeminal; the oculomotor, abducens, facial and acoustic nerves may also be affected and it is of interest to consider the causation of this disturbance in the case of these other nerves. The oculomotor nerve is commonly involved in the tentorial pressure cones associated with supratentorial masses; the nerve is stretched before and compressed by the descending hypocampal gyrus. As has been seen, the abducens may be involved in cases of supratentorial tumour by downward displacement of the brain-stem and stretching of the vertical nerve trunk; or with subtentorial masses causing swelling of the brain-stem, the trunk of the nerve may be compressed by transversely directed branches of the basilar artery which cross it. Involvement of the seventh and eighth nerves had occurred in three of the seven cases reported by Paillas *et al.* In Cushing's cases of acoustic neurinoma involvement of the contralateral eighth nerve was common and D'Errico (1950) also reported this in his series of posterior fossa meningiomata. The fact that the seventh and eighth nerves pass through the internal auditory meatus and along a bony canal may make them subject to compression on the margins of the meatus when the brain-stem is displaced; such an explanation would be analogous to that here proposed for the trigeminal false localizing signs.

The discussion has so far been limited to unilateral or bilateral trigeminal disturbance which it is believed is brought about by the movement of the brain-stem and cerebellum relative to the tentorial incisura. This sign was associated with extremely severe headache and high papillœdema in the three cases described and should perhaps be regarded as a warning of the dangers of the early development of severe brain-stem compression by a large ascending transtentorial pressure cone. Thus Castellano and Ruggiero (1953) emphasize that they, like other authors, found that with meningiomas of the cerebellar fossa signs of intracranial hypertension were constant, early and pre-eminent; cranial nerve disturbance occurred late. Cushing and Eisenhardt (1938), D'Enrico (1950) and Knupling and Fuchs (1975) have pointed to the signs of brain-stem compression in cases of posterior fossa meningiomata. Such signs were present in Case 3 here reported and also probably in Case 4. More dramatic were symptoms suggesting brain-stem compression including a different type of bilateral trigeminal disturbance in Case 5. These features will now be briefly described.

The patient with the meningioma beneath the temporo-occipital lobe (Case 4) experienced recurring attacks of paræsthesiæ in the hands of fifteen minutes' duration; later, stiffness and weakness of the legs with marked neck stiffness were added to the attacks. It is considered that this combination of intermittent symptoms resulted from compression and possibly stretching of the brain-stem, the likely underlying basis being transient ischæmia of the structure. In Case 5, superimposed on increasingly severe headaches were neck stiffness with attacks of paræsthesiæ in the face, arms and later in the legs. In one such attack weakness of the legs appeared associated with dyspnœa. It is believed that these intermittent attacks resulted from brain-stem compression by the pressure cone in the foramen magnum, the facial paræsthesiæ, like those in the limbs, resulting from involvement of nerve pathways within the medulla.

The hypothesis put forward is that trigeminal symptoms and/or signs in the presence of an unrelated tumour are due to displacement of the brain-stem. This occasions distortion of the sensory root of one or both trigeminal nerves—probably stretching and compression of it occurring. In the presence of tumours of the cerebellar fossa the relatively small size of the posterior fossa and the large size of the tentorial incisura encourage displacement of the brain-stem superiorly; so also does the shape of the fossa. The evidence for such displacement is clinical, radiological and pathological and it is thought it may be occasioned by supra- as well as infratentorial growths. The angulation of the trigeminal sensory root as it enters the posterior fossa as well as its antero-posterior direction in the fossa may be other factors leading to traction injury to the nerve at its dural foramen. Tumours of the cerebellopontine angle are directly related to the brain-stem displacing it to the opposite side. It is thought that this displacement may lead to stretching of the contralateral trigeminal sensory root because of its antero-posterior direction.

There may be cases in which the trigeminal disturbances in association with tumours at a distance has some other explanation. In the present series, however, and those in the literature to which reference has been made, it is thought that the explanation suggested is an appropriate one. As stated in an earlier paragraph a general rise of pressure in the posterior fossa does not provide an explanation for these signs. It does not account for the particular liability for involvement of certain cranial nerves, such as the fifth to the exclusion of others, such as the ninth, tenth, eleventh and twelfth; nor does it explain the frequency with which the nerve dysfunction is unilateral. Moreover, it is in the presence of such tumours as meningiomata and neuriomata, rather than intrinsic tumours such as cystic gliomata, that the involvement of the fifth cranial nerve is seen. This is true although the volume of the intrinsic tumours may considerably exceed that of the extrinsic ones. The greater displacement produced by tumours outside the nervous system may explain this difference. As has been seen (Case 5), high pressure in the posterior fossa can occasion attacks of paræsthesiæ in the face, arms and legs associated with loss of power. This quite different picture is doubtless due to compression of the brain-stem at the foramen magnum with long tract involvement. Likewise (Case 4) the attacks of paræsthesiæ in the limbs and stiffness of the legs which occurred were almost certainly due to brain-stem compression as a result of its displacement into the tentorial opening.

SUMMARY

This investigation of trigeminal false localizing signs is based upon a study of the literature, personal clinical experience and a consideration of certain aspects of posterior cranial fossa anatomy. From this it is concluded that these signs result from distortion of the trigeminal sensory root by brain-stem displacement and the factors responsible for the different displacements are analysed.

ACKNOWLEDGEMENTS

I am much indebted to Professor Charles Phillips in the Department of Human Anatomy, Oxford University, for his assistance with this work. The measurements of the foramen magnum and tentorial incisura and those of the volumes of the supra- and infratentorial portions of the brain were made by Dr. Keith Murray in that department. The unusual paramedian section of the head (fig. 5A) was also devised by Dr. Murray, whose assistance has been invaluable. I am also indebted to the Department of Medical Illustration, St. Bartholomew's Hospital, London.

REFERENCES

BONHOEFFER, K. (1915) Demonstration zur Pathologie der Kleinhirnbrucken-winkeltumoren. *Berliner klinische Wochenschrift*, **52**, 299–300.

CASTELLANO, F. and RUGGIERO, G. (1953) Meningiomas of the posterior fossa. *Acta Radiologica*, Suppl. 104, 77P.

COLLIER, J. (1904) The false localizing signs of intracranial tumour. *Brain*, **27**, 490–508.

CUSHING, H. (1910) Strangulation from nervi abducentes by lateral branches of the basilar artery in cases of brain tumour. *Brain*, **33**, 204–235.

—— (1917) *Tumours of the Nervus Acusticus and the Syndrome of the Cerebello-pontine Angle*. Philadelphia: Saunders, p. 162.

—— and EISENHARDT, L. (1938) *Meningiomas*. Springfield, Illinois: Thomas, p. 186.

DANDY, W. (1932) The treatment of trigeminal neuralgia by the cerebellar route. *Annals of Surgery*, **96**, 787–795.

D'ERRICO, A. (1950) Meningiomas of the cerebellar fossæ. *Journal of Neurosurgery*, **7**, 227–232.

ECKER, A. (1948) Upward transtentorial herniation of the brainstem due to tumour of the posterior fossa. *Journal of Neurosurgery*, **5**, 51–61.

FUNKENSTEIN, O. (1905) Ein Beitrag zur Kenntnis der Tumoren des Kleinhirnbruckenwinkels. *Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie*, **14**, 157–194.

Gray's Anatomy (1973) 35th Edition. Edinburgh: Longman, p. 983.

HAMBY, W. B. (1943) Trigeminal neuralgia due to radicular lesions *Archives of Surgery, Chicago*, **46**, 555–563.

—— (1947) Trigeminal neuralgia due to contralateral tumours. *Journal of Neurosurgery*, **4**, 179–192.

KNUPLING, R. and FUCHS, E. C. (1975) Meningiomas of the posterior fossa. In *Proceedings of 25th Annual Meeting of the Deutsche Gesellschaft für Neurochirurgie*. Berlin: Springer Verlag, pp. 116–120.

LE BEAU, J. (1944) La hernia du cervelet au-dessus du tentorium. *Union Médicale du Canada*, **73**, 243–252.

LYSHOLM, E. (1939) Ventriculography of the fourth ventricle. *American Journal of Roentgenology*, **41**, 18–24.

NORTHFIELD, D. W. C. (1973) *The Surgery of the Central Nervous System*. Oxford: Blackwell, p. 32

O'CONNELL, J. E. A. (1956) The place of surgery in the treatment of cervical spondylosis. *Proceedings of the Royal Society of Medicine*, **49**, 202–208.

PAILLAS, J. E., PELLET, W., JANNY, P., TOURNILHAC, M. and KOMMINOTH, J. (1969) L'atteinte contralaterale des nerfs craniens au cours des tumeurs de la fosse postérieure. *Revue Neurologique*, **121**, 452–464.

PARKER, H. L. (1928) Tumours of the nervus acusticus. Signs of involvement of the fifth cranial nerve. *Archives of Neurology and Psychiatry*, **20**, 309–318.

—— (1937) Paroxysmal trigeminal neuralgia with tumours of the nervus acusticus. *Journal of Neurology and Psychiatry*, **17**, 256–261.

RUCH, J. C. and PATTON, H. D. (1965) *Physiology and Biophysics*. Philadelphia: Saunders, p 938.

SUNDERLAND, S. (1957) The tentorial notch and complications by herniations through that aperture. *Journal of Neurosurgery*, **45**, 422–438.

TWINING, E. W. (1939) Radiology of third and fourth ventricles. *British Journal of Radiology*, **12**, 385–418; 567–598.

UHTHOFF, O. (1906) In: *Graefe-Saemisch Handbuch der gesamten Augenheilkunde.* Zweite auflage, Leif 105–108. Bd xi, KAP xxii, 2 Teil, S 567.

WEISENBURG, F. (1910) Cerebellopontine tumour diagnosed for six years as *tic douloureux. Journal of the American Medical Association,* **44,** 1600–1604.

(*Received July 12, 1977*)

Brain (1978), **101**, 143-162

FOCAL CONTRALATERAL MYOCLONUS PRODUCED BY INHIBITION OF GABA ACTION IN THE CAUDATE NUCLEUS OF RATS

by D. TARSY,[1] C. J. PYCOCK, B. S. MELDRUM *and* C. D. MARSDEN

(*From the University Department of Neurology, Institute of Psychiatry, and King's College Hospital Medical School, London SE5*)

INTRODUCTION

RECENT post-mortem biochemical investigation of Huntington's chorea suggests that loss of γ-aminobutyric acid (GABA) action in the basal ganglia may result in abnormal involuntary movements (dyskinesias). The concentrations of GABA and of its synthesizing enzyme, glutamic acid decarboxylase (GAD), are considerably reduced in certain of the basal ganglia compared with levels in normal brains (Perry, Hansen and Kloster, 1973; Bird, Mackay, Rayner and Iversen, 1973; McGeer, McGeer and Fibiger, 1973*a*, *b*; Bird and Iversen, 1974; Bird, 1976). Loss of GABA in the corpus striatum (caudate nucleus and putamen) reflects the extensive loss of striatal neurons that is the characteristic pathology of the disease. Loss of GABA in substantia nigra and globus pallidus may reflect loss of strio-nigral and strio-pallidal pathways. The changes in GABA appear restricted to the basal ganglia, for cerebral cortical GABA and GAD levels are normal, despite extensive cortical cell loss. Accordingly, failure of GABA synthesis is not a fundamental biochemical deficit in Huntington's chorea; it appears to be a consequence of death of basal ganglia GABA neurons, particularly those in the corpus striatum. However, the changes in basal ganglia GABA in Huntington's chorea do suggest that alteration in the activity of this neurotransmitter may cause dyskinesias.

In the course of a study of the behavioural effects of manipulating GABA activity in the basal ganglia, we found that the direct injection of picrotoxin, a GABA antagonist (Precht and Yoshida, 1971; Hill, Simmonds and Straughan, 1973) into one caudate nucleus of the rat caused sustained myoclonic jerks of the opposite limbs. In this paper we describe pharmacological experiments designed to test whether this myoclonus is the result specifically of interference with striatal GABA action, and physiological experiments designed to establish the source of the myoclonus. Preliminary reports of this work have been published elsewhere (Marsden, Meldrum, Pycock and Tarsy, 1975; Pycock, 1976).

---

[1] Present address: Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA

METHODS

Preparation of Animals

Male and female Wistar rats (200–250 g) were anæsthetized with chloral hydrate (300 mg/kg, i.p.) or methohexitone sodium (50–100 mg/kg) and immobilized in a Stoelting stereotaxic frame. In most animals either unilateral or bilateral stainless steel guide cannulæ (outer diameter, 0·75 mm; inner diameter 0·4 mm; length 7 mm) were mounted vertically into burr holes drilled into the skull directly over the anterior caudate nucleus, posterior caudate nucleus, globus pallidus, thalamus, or the ventral hippocampus. The co-ordinates were taken from the atlas of König and Klippel (1963) (anterior caudate nucleus A 8·5 L ∓ 2·5; posterior caudate nucleus A + 6·7, L ∓ 3·8; globus pallidus A + 6·3, L ∓ 2·5, thalamus, A + 2·4, L ∓ 2·0; ventral hippocampus A + 2·4, L ∓ 4·0). The guide cannulæ were set just above the surface of the brain so that the end of the cannula did not damage the cortex below, and were held in position with acrylic dental cement.

A few animals were also prepared with bilateral angled guide cannulæ pointing towards the centre of the caudate nucleus. These cannulæ were mounted at the co-ordinates A + 3·7, L ± 2·5, and set at an angle of 45 degrees pointing anteriorly. In addition to these angled guides, a unilateral guide cannula was sometimes mounted in the skull vertically over the anterior caudate nucleus on one side of the brain. The latter cannula guide was allowed to penetrate the surface of the cortex in such animals.

Experimental Procedure

Animals were allowed at least 24 h for recovery. Injections were always made in hand-held conscious animals with a Hamilton syringe fitted with a 701 N needle. A nylon cuff around the needle acted as a stop and served to govern the depth of injection. The vertical co-ordinates chosen for the various regions were: cortex (directly overlying the caudate nucleus) V + 3·5; anterior and posterior caudate nucleus area V 0; globus pallidus V — 1·0; thalamus V — 0·4; ventral hippocampus V — 2·4 (König and Klippel, 1963). Following intracerebral injections, animals were placed individually in plastic boxes measuring 35 × 25 cm, and their motor behaviour was observed for periods up to 2 h.

Unilateral Injection of GABA Antagonists

Picrotoxin (0·1 – 2 μg dissolved in 1 – 3 μl 0·9 per cent saline) was injected unilaterally into the cortex, caudate nucleus, globus pallidus, thalamus, and hippocampus, or bilaterally into the region of the anterior caudate nucleus and globus pallidus, and the effects on motor behaviour were observed. Also angled injections of picrotoxin (0·5 - 1 μg) into the caudate nucleus were studied. Control injections of physiological saline (2 μl) were made into all sites.

In addition to picrotoxin, the effects of other GABA antagonists injected into one striatum of the rat were studied. DL-allylglycine (50–200 μg in 2–3 μl 0·9 per cent saline), bicuculline (1–3 μg) and benzyl-penicillin (1 unit in 2 μl) were injected unilaterally into the region of the anterior caudate nucleus through a vertical cannula. (Bicuculline was dissolved in a minimum amount of 0·1 N HCL, pH adjusted to 6·5 with 0·1 N NaOH and the solution made up to volume with saline).

Unilateral Injection of GABA Agonists

In another series of animals, the effect of GABA and its agonist DL-carnitine (γ-amino-β-hydroxybutyric acid) injected into one caudate nucleus was studied. GABA (100–750 μg in 3 μl 0·9 per cent saline) or carnitine (250 or 500 μg in 2 μl 0·9 per cent saline) were either given alone or injected into the striatum following either picrotoxin or allylglycine.

Effect of Drugs on Picrotoxin Response

Rats with unilateral cannulæ were injected intraperitoneally with a number of drugs known to affect various central neuronal mechanisms. At a time when such agents were exerting maximal effects, picrotoxin (0·75 μg) was injected into the anterior region of one caudate nucleus and the motor responses observed. Control responses were monitored in the same animals previously injected with saline intraperitoneally. The following pre-treatments were administered at the times stated prior to picrotoxin L-5-hydroxytryptophan (Sigma Ltd) (50 and 500 mg/kg, i h), methysergide (Sandoz Ltd) (5 mg/kg, 1 h); reserpine (Ciba-Geigy Ltd) (10 mg/kg, 4 h); L-dopa (Roche Ltd) (100 mg/kg, 1 h) together with the peripheral decarboxylase inhibitor, carbidopa (Merck Sharp and Dohme Ltd) (25 mg/kg, 30 min before L-dopa): chlorpromazine (May and Baker Ltd) (10 mg/kg, 1 h); haloperidol (Searle) (2 mg/kg, 1 h); d-amphetamine (Smith, Kline and French) (3 mg/kg, 30 min); clonidine (Boehringer) (0·5 mg/kg, 1 h), and scopolamine (Sigma Ltd) (10 mg/kg, 1 h). The time to onset of the first myoclonic jerk and the duration of the response were noted, together with the frequency of the jerks recorded in a one-minute period 30 min after picrotoxin injection. The intensity of the response during the course of the experiment was judged as being strong, moderate or weak.

Unilateral Globus Pallidus Lesions

Unilateral electrolytic lesions were placed in the region of the globus pallidus in 10 rats. A single lesion was aimed at the centre of the pallidum (A + 6·5 L ± 2·4 V − 1·0) in half of these animals by lowering an electrode, varnished except for the tip, to the correct depth, and passing a current of 5 mA for 4 s. The negative electrode was attached to the ear. In the other 5 rats, two electrolesions (10 mA for 8 s) were placed in the region of the pallidum, one at the anterior position (A + 6·8 L ± 2·3 V − 1·2), the other at the posterior position (A + 5·9 L ± 3·3. V − 1·4). In both these groups of rats with lesions a guide cannula was mounted over the anterior portion of the ipsilateral striatum and held by dental cement in the usual way.

The motor response to the intrastriatal administration of picrotoxin (0·75 and 1 μg) was observed subsequently. The extent of the pallidal lesions was judged histologically and pharmacologically. The circling response of these rats to d-amphetamine (4 mg/kg) and apomorphine (0·5 mg/kg, s.c.) was used to assess the extent of pallidal damage.

Histological Examination of Injection Site

After animals had been used for a maximum of four focal injections into the same brain site, they were killed and the brains fixed in formol-saline for at least a week. Brains were examined both macroscopically and histologically for the identification of the needle track and verification of the target areas. Those animals in which the needle tip had missed the intended areas, or was close to adjacent structures which would in turn be affected by diffusion of the injected drugs, were discarded from the experimental data.

EEG Recordings

In other experiments electrical activity was monitored from the caudate nucleus and cerebral cortex during the injection of drugs into the striatum. Such animals were prepared with screws set in the skull which ended on the surface of the cortex. Striatal activity was recorded from needle electrodes, varnished except for the tip, and inserted through the guide cannulæ into the left and right caudate nuclei

RESULTS

Unilateral Intracerebral Injections (*Vertical*) *of Picrotoxin*

(1) *Caudate nucleus.* The injection of saline into any of the brain regions investigated in this study never caused any sustained abnormal motor activity. When saline was administered into either one caudate nucleus or globus pallidus, the penetration of the needle into the brain was sometimes accompanied by the development of a transient contralateral body asymmetry and weak irregular contraversive circling. Such motor activity, however, lasted only 2–3 min.

Unilateral injection of picrotoxin (0·5 - 1·5 μg in 1 - 3 μl 0·9 per cent saline) into the caudate nucleus of the rat resulted in a rhythmic jerking movement of the contralateral limbs. This jerking motion has been termed 'focal myoclonus' (Marsden *et al.*, 1975), being reminiscent of the human syndrome. The myoclonus observed commenced 4–9 min following picrotoxin injection (mean 5·8 ± 0·7 min, 20 animals) and lasted approximately 45–80 min (mean 52·0±3·6 min). The time of onset and duration of myoclonus was approximately the same irrespective of the dose of picrotoxin.

The myoclonus consisted of a sharp contraction of the flexor muscles of one limb, lifting it off the ground, followed by a somewhat slower phase of relaxation. Each jerk lasted a fraction of a second, but jerks occurred repetitively and rhythmically every 5–12 s. Between jerks the limb digits often remained flexed and on occasions the whole limb might be kept elevated off the floor surface. However, the animals apparently suffered no other obvious disability and would resume normal activity between the jerks such as grooming or washing. The flexed posture of the digits and limbs sometimes appeared some 2–3 min before jerking began. Almost always the myoclonus was monophasic, but occasionally a double jerk pattern was observed, and rarely (during the later part of the picrotoxin effect) the jerks built up in frequency merging into a sustained focal clonic seizure lasting a matter of some minutes, followed again by repetitive rhythmic jerks. Myoclonus often remained confined to one contralateral limb, but sometimes spread during the course of the experiment to other regions of the body. Thus forelimb myoclonus subsequently involved the neck and head, the latter being pushed up and away from the jerking limb, while a hindlimb myoclonus often involved the lower trunk region. Such a spread of myoclonus was probably associated with diffusion of the drug through the striatum, although no direct studies were made to verify this. On occasions a single picrotoxin injection would cause jerks of both the opposite arm and leg, which would throw the rat to the opposite side. On such occasions the animal usually took refuge at the side of the cage for support.

The distribution of myoclonus in response to intra-caudate injections of picrotoxin is shown in Table 1. In general, injection into the anterior part of the caudate nucleus (fig. 1) caused jerks of the opposite forelimb and also sometimes of the head and neck. Injection into the posterior part of the caudate nucleus (fig. 2) caused jerks of the opposite hindleg.

TABLE 1. DISTRIBUTION OF MYOCLONUS IN RATS FOLLOWING UNILATERAL INJECTIONS OF PICROTOXIN (0·5 - 1·5 μg) INTO CAUDATE NUCLEUS

Site of injection	*No. of rats*	*No. of injections*	*Site of myoclonus (always contralat.)*	*Incidence*
Anterior caudate	20	27	Forelimb	11
			Head, neck and forelimb	8
			Forelimb, trunk and hindlimb	5
			Head, neck and both limbs	1
			Trunk	1
			Hindlimb	1
Posterior caudate	10	10	Trunk and hindlimb	7
			Hindlimb	3

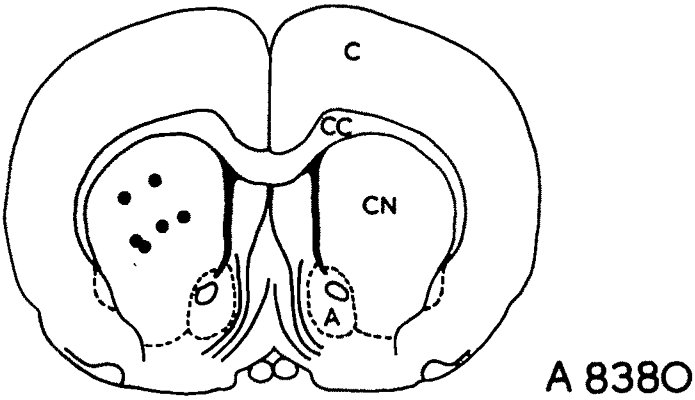


FIG. 1. Diagram of coronal section through the region of the anterior caudate nucleus to show sites of injection of drugs in 6 animals. In this and subsequent figures, A = nucleus accumbens, C = cerebral cortex, CC = corpus callosum, CN = caudate nucleus, GP = globus pallidus, H = hippocampus, SN = substantia nigra, and T = thalamus.

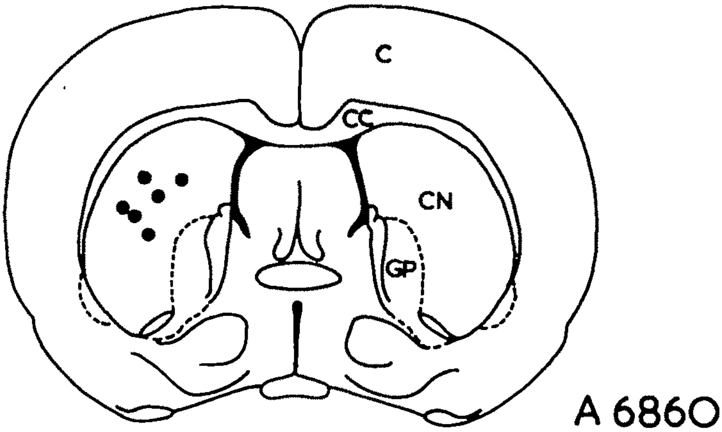


FIG. 2. Diagram of coronal section through the region of the posterior caudate nucleus to show site of injection of drugs in 6 animals.

Unilateral injection of small doses of picrotoxin (0·1 and 0·25 μg in 2 μl 0·9 per cent saline) in 10 animals into the striatum was usually ineffective in producing limb myoclonus. The majority of animals behaved normally: only some 5 to 10 per cent of those injected developed faint muscular twitches of the head and neck. High doses of picrotoxin (2 μg) injected into the striatum of 3 animals resulted in generalized seizures. Postural deviation was not produced following unilateral striatal injection of any dose of picrotoxin and sustained circling behaviour was never seen.

(2) *Other sites.* Injection of picrotoxin (0·5–1·5 μg in 2 μl saline) into the cortex overlying the striatum rarely resulted in contralateral limb myoclonus. Only 3 of 20 such animals developed any form of myoclonic twitch. Two rats developed contralateral forelimb myoclonus after 9 and 15 min respectively, while the third animal showed facial twitches and spasms after 8 min. All 20 animals subsequently developed contralateral limb myoclonus when the same dose of picrotoxin was injected directly into the striatum.

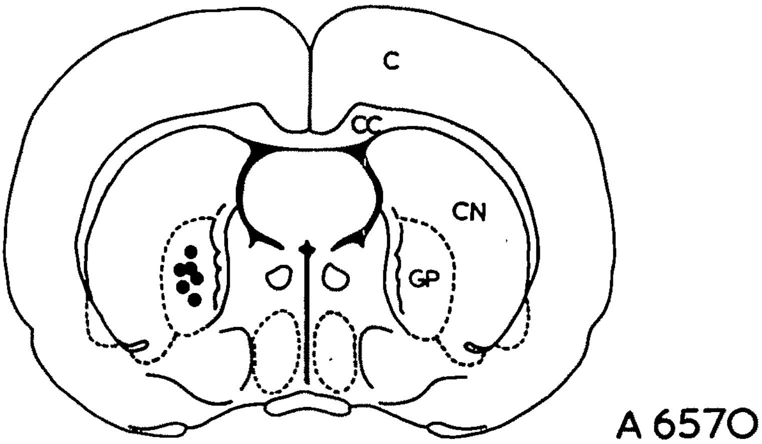


FIG. 3. Diagram of coronal section through the region of the globus pallidus to show site of injection of drugs in 6 animals.

Injections of picrotoxin (0·5 – 1 μg) into one globus pallidus (fig. 3) in 8 rats caused increased locomotor activity; the animal would run or pace around the observation cage. Such activity began some 8–12 min after picrotoxin injection and lasted intermittently for periods of up to one hour. Circling behaviour and body asymmetry were not observed. Occasionally (in 3 of 8 animals) the hyperactivity was accompanied by characteristic myoclonic jerks of the contralateral hindlimb/lower trunk region. These jerks were similar in onset, character and duration to those seen after the injection of picrotoxin into the posterior region of the caudate nucleus, suggesting that they were the result of diffusion of picrotoxin into the adjacent striatum. Low doses of picrotoxin (0·1 and 0·25 μg) injected into one globus pallidus had no effect; high doses (1·5 μg) caused generalized seizures.

Injection of picrotoxin into either the thalamus (in 4 rats) or ventral hippocampus (in 4 rats) caused no myoclonic response. Low doses (0·1 and 0·25 μg) were completely without effect; higher doses (0·5 and 1 μg) resulted in generalized body seizures.

Bilateral Intracerebral Injections of Picrotoxin

Bilateral injection of picrotoxin (1 μg) into the anterior region of both caudate nuclei caused a repetitive myoclonus characterized by synchronized flexion and extension of both forelimbs together with an extension of the head: a syndrome reminiscent of retrocollis in the human. Such an effect often produced violent limb contractions, so much so that the animal was forced upright on its haunches and on occasions was thrown over backwards by the strength of the contractions. The time of onset after picrotoxin injection of this myoclonus was similar to that after unilateral injections, although its duration of approximately 90 min was slightly longer.

Bilateral injections of picrotoxin (0·1 - 1 μg) into the region of the globus pallidus resulted in a dose-dependent effect on motor behaviour characterized by mild twitching at the low dose, bilateral limb jerks at the middle dose, and hyperactivity and generalized seizures with the high dose. These results have been described elsewhere (Pycock, Horton and Marsden, 1976).

Unilateral Intrastriatal Injections of other GABA Antagonists

DL-c-allylglycine (100–150 μg in 2–3 μl 0·9 per cent saline), an inhibitor of glutamic acid decarboxylase, often caused myoclonus similar to that described for picrotoxin when injected into one striatum (15 rats). Myoclonic jerks of the contralateral limbs, neck and head commenced some 45 min after injection (range 20–55 min; mean 46·7 ± 7·4 min); the jerking lasted 65–200 min. Such myoclonus occurred in 2 of 6 experiments with 100 μg, in 3 of 4 experiments with 125 μg, and in 7 of 12 experiments with 150 μg. On one occasion repetitive forelimb jerks built up into repeated focal seizures.

Bicuculline, a GABA receptor blocking agent (Curtis, Duggan, Felix, Johnston and McLennan, 1971), in doses of 1–2 μg, induced a weak contralateral myoclonus with the time of onset comparable to that after picrotoxin (mean 8·4 ± 0·8 min; N = 5) but with a shorter duration of approximately 10–15 min (mean 12·2 ± 1·5 min; N = 5). (Control injections of vehicle caused no such movements). Subsequent injections of picrotoxin (1·0 μg) into the same site in these animals resulted in characteristic jerking of the same contralateral limb as had been observed following bicuculline, but the intensity of the myoclonus after picrotoxin was greater.

Benzylpenicillin induced a weak contralateral limb myoclonus in 2 of 4 animals after a latency of 9–12 min. The jerks were similar to those after picrotoxin, but were much weaker, more irregular and of a shorter duration. Benzylpenicillin produced no motor effects in the other 2 animals.

Unilateral Intrastriatal Injections of GABA and Carnitine

Neither GABA (100–750 μg) nor carnitine (250–500 μg) administered alone into one striatum induced myoclonus or abnormal behavioural response (other than that previously described for the saline injections).

GABA (100–750 μg in 2 μl 0·9 per cent saline) was injected into one caudate nucleus 10–20 min after picrotoxin (0·5–1 μg) had been administered into the same site to cause the typical contralateral myoclonus. The picrotoxin-induced myoclonus stopped abruptly some 2–3 min after the GABA injection in 7 of the 9 animals. In the remaining 2 animals, the doses of GABA injected (250 and 500 μg respectively) had no effect. The jerks did not recur on 6 of 7 occasions in which the GABA stopped picrotoxin-induced myoclonus, but in the remaining experiment the jerks reappeared 40 min later. Injection of GABA (100–750 μg in 2 μl 0·9 per cent saline) 60–85 min after dl-c-allylglycine (150 μg) into one caudate nucleus stopped allylglycine-induced myoclonus within 2 min in 6 of 7 rats. The jerks returned on 3 occasions after some 60–120 min and persisted for a further 60–120 min.

Control injections of saline in similar circumstances had no effect in abolishing or reducing drug-induced myoclonus.

In another series of experiments using animals in whom contralateral myoclonus had been produced by picrotoxin injection into the anterior caudate nucleus, carnitine (γ-amino-β-hydroxybutyric acid, 250–500 μg in 2 μl 0·9 per cent saline) was injected into the same site 15–18 min after picrotoxin. Carnitine abolished picrotoxin-induced myoclonus in 3 of the 6 animals within 2–5 min. The myoclonic jerks ceased in 2 of these 3 animals for 23 and 45 min respectively and then recurred; in the third rat myoclonus never reappeared. Carnitine had no effect on picrotoxin-induced myoclonus in 2 animals, and in the remaining animal it decreased the amplitude and frequency of the jerks but did not abolish them.

Unilateral Angled Injection Studies

Angled injections of picrotoxin (1 μg in 2 μl 0·9 per cent saline) into the centre of one caudate nucleus produced no myoclonus or other behavioural response in 8 rats in which no vertical cannulæ were inserted into the cerebral cortex. Subsequent vertical injections of picrotoxin (1 μg) into one striatum in these animals through cannula guides, set above the cortex, resulted in the usual contralateral limb myoclonus.

Angled injection of picrotoxin into the centre region of one caudate nucleus in animals in which a vertical cannula guide had also been set into the surface of the cerebral cortex resulted in the development of the familiar contralateral limb myoclonus. The results are summarized in Table 2. In all experiments the position of the needle tip was verified by histological examination (fig. 4).

TABLE 2. COMBINATION OF VERTICAL AND ANGLED INJECTIONS OF PICROTOXIN (1 μg) INTO THE CAUDATE NUCLEUS FOR THE INDUCTION OF CONTRALATERAL LIMB MYOCLONUS IN THE RAT

		Myoclonus			
Injection path	*No. of rats*	*Incidence*	*Mean onset (min ± 1 SEM)*	*Mean duration (min ± 1 SEM)*	*Intensity (0 – 3+)*
Vertical into cortex only	20	3	—	—	—
Vertical into striatum	20	20	5·8 + 0·7	52·0 + 3·6	++
Angled into striatum (no cortical cannula)	8	0	—	—	—
Angled into striatum (presence of cannula set in cortex)	8	8	7·7 + 0·9	47·9 + 3·5	++

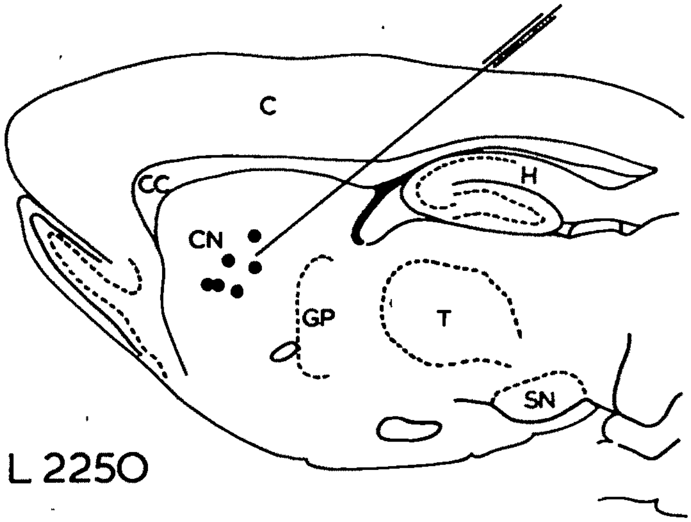


FIG. 4. Diagram of saggital section to show sites of angled injection of drugs into caudate nucleus in 6 animals

Effect of Various Drugs of Picrotoxin-induced Myoclonus

The effect of a number of systemically administered drugs on the myoclonic response induced by unilateral intrastriatal injection of picrotoxin is shown in Table 3. In summary, few of the compounds caused any change in the time of onset, duration, frequency or intensity of the contralateral limb myoclonus seen after picrotoxin. Only reserpine and scopolamine produced statistically significant effects, reserpine prolonging the duration of the effect (from 53 to 72 min, $P < 0{\cdot}05$) and increasing the myoclonic frequency and intensity, while scopolomine delayed the onset from 9 to 16 min ($P < 0{\cdot}001$), and decreased the frequency and intensity of the picrotoxin effect. No changes were observed with the other compounds tested.

TABLE 3. THE EFFECT OF PRE-TREATMENT WITH VARIOUS DRUGS ON CONTRALATERAL LIMB MYOCLONUS INDUCED IN THE RAT BY THE UNILATERAL INTRACAUDATE INJECTION OF PICROTOXIN (1 μg)

Pre-treatment (and dose)	*No. of rats*	*Time to onset (min ± 1 SEM)*	*Duration (min ± 1 SEM)*	*Myoclonic frequency (Jerks/min)*	*Myoclonic intensity*
0	11	8·7 ± 0·8	53·5 ± 5·4	6·1 ± 0·7	++
5-hydroxytryptophan (50 mg/kg)	4	11·0 ± 1·1	57·7 ± 4·5	4·1 ± 1·4	++
5-hydroxytryptophan (200 mg/kg)	6	8·0 ± 1·2	59·5 ± 6·2	5·2 ± 1·2	++
Methysergide (4 mg/kg)	6	9·3 ± 0·8	56·5 ± 7·7	10·5 ± 2·4	++
Reserpine (10 mg/kg)	6	7·3 ± 1·4	72·2 ± 7·5*	10·0 ± 1·2*	+++
α-methyl-*p*-tyrosine (250 mg/kg)	6	11·0 ± 1·9	52·8 ± 7·3	5·8 ± 0·7	++
L-dopa + carbidopa (100 mg/kg)	6	9·2 ± 1·2	52·8 ± 9·5	5·1 ± 0·1	++
Chlorpromazine (10 mg/kg)	6	8·3 ± 1·2	57·0 ± 8·9	5·4 ± 1·6	++
Haloperidol (2 mg/kg)	5	8·6 ± 2·8	50·0 ± 2·7	4·8 ± 1·2	+++
Clonidine (0·5 mg/kg)	4	12·0 ± 2·8	50·3 ± 6·4	6·3 ± 1·2	++
Amphetamine (3 mg/kg)	4	8·7 ± 0·6	49·0 ± 5·1	5·2 ± 1·0	++
Scopolamine (10 mg/kg)	5	16·0 ± 1·9**	41·0 ± 3·3	4·1 ± 0·4*	+

Mean ± 1 SEM is shown. Significance (Student's t test of paired samples) * $P < 0{\cdot}05$, ** $P < 0{\cdot}001$. The intensity of myoclonus is assessed on a 0 - 3 scale, where 0 is nil, and +++ is maximum.

Thus, blockade of central catecholaminergic mechanisms by inhibition of synthesis with α-methyl-p-tyrosine or by receptor blockade by haloperidol or chlorpromazine, did not alter the time of onset, intensity or duration of picrotoxin-induced myoclonus. Similarly, stimulation of central catecholaminergic mechanisms by administration of either L-dopa or d-amphetamine had no significant effect on the myoclonus. Stimulation of central α-adrenoceptors with clonidine had no effect.

Manipulation of brain 5-hydroxytryptamine, either by stimulation through the administration of 5-hydroxytryptophan, or by blockage of 5-HT receptors with methysergide, did not significantly alter the picrotoxin-induced myoclonic response.

Effect of Lesions of the Globus Pallidus on Picrotoxin-induced Myoclonus

Single electrolytic lesions placed in the region of one globus pallidus in 4 of 5 animals did not prevent the myoclonus induced by an injection of picrotoxin into the anterior region of the ipsilateral caudate nucleus. The time of onset and the duration of the response did not differ significantly from that observed in control animals. Subsequent histological examination of the brains from these rats revealed that the damage to the globus pallidus was only partial, usually being confined to the medial area. Using a stage micrometer it was judged that in these animals some 65 to 75 per cent of the pallidum had been destroyed (fig. 5). Histologically intact areas of the globus pallidus could still be identified. These animals exhibited some irregular ipsiversive circling response to both systemically-administered apomorphine and d-amphetamine.

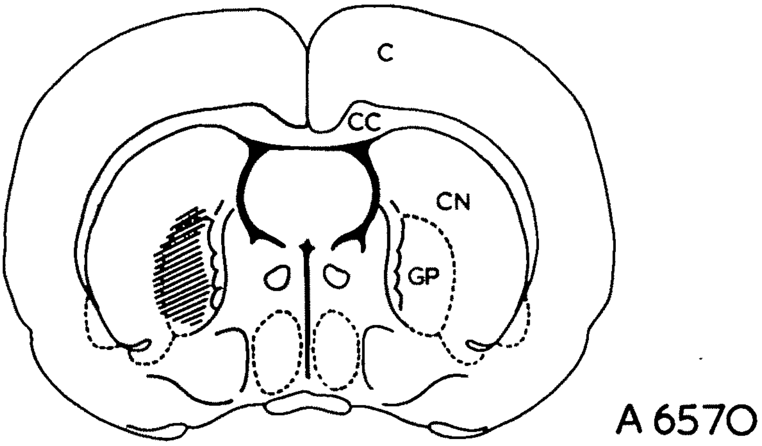


FIG 5. Diagram of coronal section to show extent of destruction of one globus pallidus produced by a single electrolytic lesion in 5 animals

Two large electrolytic lesions placed in the anterior and posterior regions of one globus pallidus completely abolished the myoclonic response normally seen after injection of picrotoxin into the ipsilateral striatum. No motor response was observed in these 5 animals. Histologically one globus pallidus in each animal had been completely destroyed, but damage also involved the adjacent areas of the posterior caudate nucleus and internal capsule, and sometimes the overlying cortex and hippocampus, and parts of the thalamus (fig. 6). Damage extended up to 0·5 mm outside the pallidum. These animals showed strong ipsiversive circling response to both apomorphine and d-amphetamine.

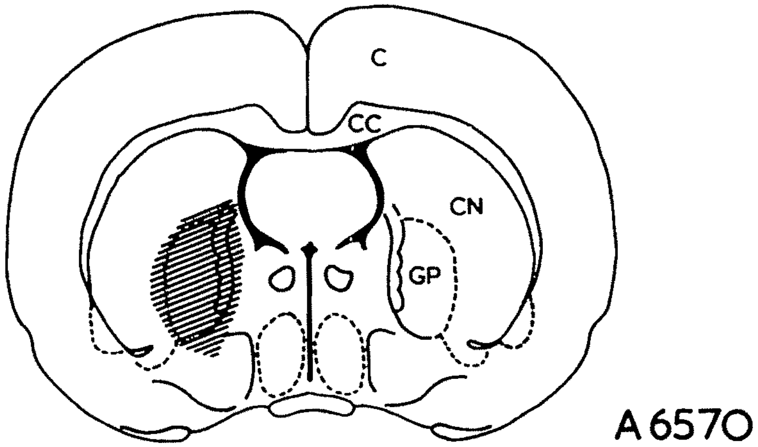


FIG. 6. Diagram of coronal section to show extent of destruction of one globus pallidus and adjacent structures produced by two electrolytic lesions in 5 animals.

Cortical and Striatal EEG Recordings

EEG recordings made from rats showing contralateral myoclonic limb jerks in response to intrastriatally-administered picrotoxin or allylglycine are illustrated in fig. 7. Traces were made using cortical and striatal electrodes. Spikes representing seizure activity were recorded from the striatum for several minutes before they could be observed in the electrocorticogram. Striatal spikes occurred before the onset of limb myoclonus and continued regularly throughout the duration of the motor effect. The spikes were abolished temporarily after the intrastriatal administration of GABA, which subsequently inhibited the jerks themselves. As the GABA effect wore off, both striatal spikes and contralateral limb myoclonus returned.

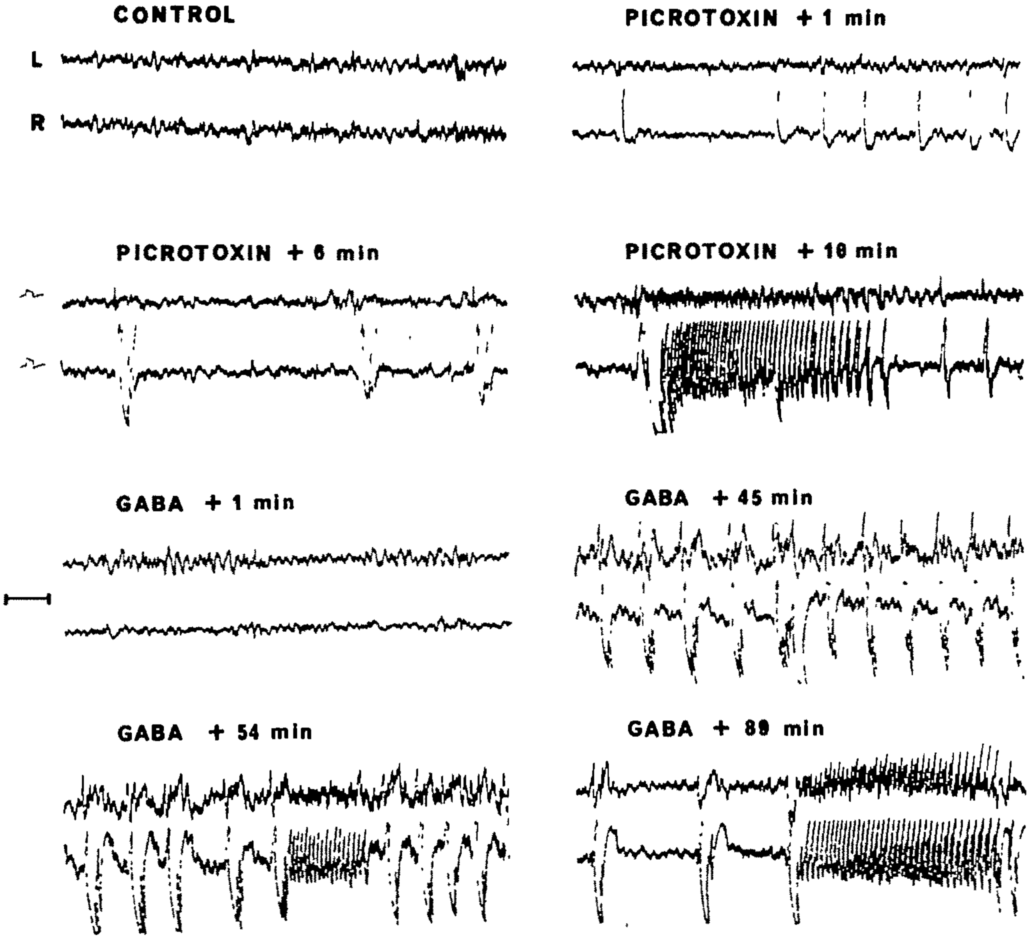


FIG. 7A. EEG records from a rat after unilateral injection of picrotoxin and then GABA into the right striatum Control-bipolar recordings between left (L) and right (R) striatum and the ear. One min after picrotoxin (0·75 μg in 2 μl) was injected into the right striatum focal spikes were recorded in the absence of any motor activity. After 6 min triple spikes occurred in association with left fore- and hindlimb jerks. Subsequently bursts of spikes were accompanied by clenching and twitching of the left forelimb. GABA (500 μg in 2 μl) was injected into the right striatum 12 min after the picrotoxin injection. Focal spikes and limb jerks were absent for 40 min, but returned, and were more sustained after 45 min than before GABA injection Subsequently, bursts of spikes associated with a raised left forelimb were frequent. Calibrations 50 μV and 1 s.

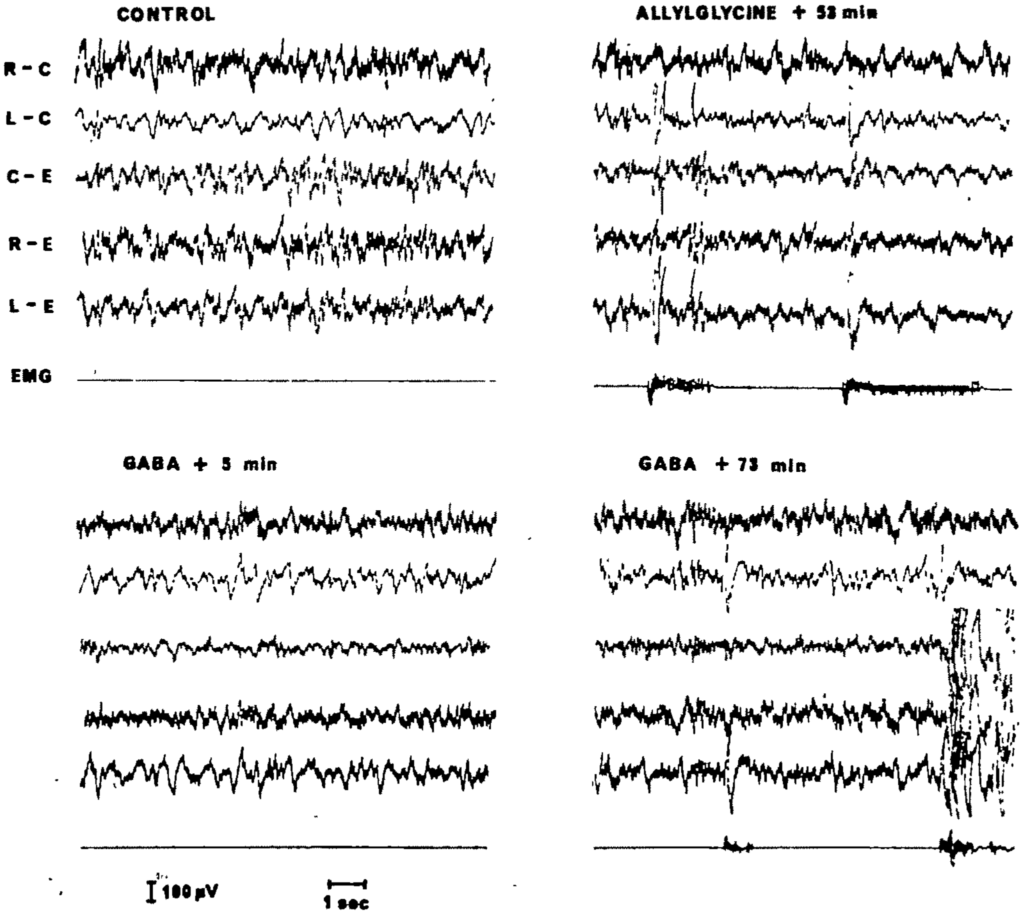


FIG. 7B. EEG and EMG records from a rat after unilateral injection into the left striatum. Control: bipolar EEG records from right striatum-cortex (R — C), left striatum — cortex (L — C), cortex — ear (C — E), right striatum — ear (R — E), left striatum — ear (L — E), and EMG from right hindlimb hip flexors. Allylglycine (150 µg in 2·5 µl 0·9 per cent saline) was injected into the left striatum. Jerks of the right hindlimb and focal spikes in the left striatum and cortex occurred after 40 min. GABA (250 µg in 2·0 µl 0·9 per cent saline) was then injected into the left striatum 62 min after allylglycine. The focal spikes and limb jerks ceased in 4 min, but reappeared 25 min later.

DISCUSSION

Characteristics of the Myoclonus

The myoclonus provoked by intracaudate injection of picrotoxin and other agents was characterized by brief, abrupt, repetitive contractions of the muscles, predominantly the flexor muscles of the contralateral limbs. The muscle jerks resembled the myoclonus seen in certain neurological diseases. Like the myoclonus in Creutzfeldt-Jakob disease and subacute sclerosing panencephalitis, or that which typifies epilepsia partialis continua, the jerks were rhythmically repetitive every few seconds. On occasion the jerks built up in frequency to produce what appeared to be a short-lived focal motor seizure, but with no apparent loss of consciousness.

The myoclonus produced by intracaudate injection of picrotoxin is probably identical to the abnormal movements described by McKenzie, Gordon and Viik (1972) after injection of d-tubocurarine into the striatum of the rat. McKenzie *et al.* characterized these dyskinesias as 'chorea', but from their description they appear similar to the myoclonus observed in the present study. D-tubocurarine resembles picrotoxin in possessing the capacity to prevent the inhibition of single neurons produced by iontophoretic application of GABA to Renshaw cells (Curtis, Game and McCulloch, 1974). Thus d-tubocurarine blocks GABA action, although it is not very potent or selective in this respect. In a subsequent paper, McKenzie and Viik (1975) established that picrotoxin produced the same type of myoclonus as d-tubocurarine when injected into one striatum, but that smaller doses were required.

Source of the Myoclonus

At first sight the myoclonus produced by injection of picrotoxin into one caudate nucleus would appear to originate in that structure. Certainly injection of similar amounts of picrotoxin into the globus pallidus, thalamus or hippocampus did not cause myoclonus, and injection into the cerebral cortex overlying the head of caudate did so only rarely. However, the cannulæ and injection needles placed vertically into the caudate nucleus, passed through the cerebral cortex, and specifically through the sensorimotor cortex which overlies the caudate nucleus in the rat (Hall and Lindholm, 1974). The occasional appearance of what appeared to be a typical focal motor seizure of the contralateral limbs made us suspicious that the myoclonus produced by intracaudate injection of picrotoxin was really a cortically-induced phenomenon, resulting perhaps from diffusion of the picrotoxin back up the needle track into the overlying sensorimotor cortex. But we could not reproduce the phenomenon by direct injection of picrotoxin into the cerebral cortex at the same site.

For these reasons, we set up experiments to inject picrotoxin into the caudate nucleus through cannulæ angled at 45 degrees to penetrate the cerebral cortex at a different site, specifically not through the sensorimotor cortex. To our surprise such angled injections into the caudate did not cause myoclonus, which initially suggested that the caudate could not be the site of the origin of picrotoxin-induced myoclonus.

The dilemma may be resolved by the final experiment in the series in which picrotoxin was delivered into the caudate nucleus through angled cannulæ, but, in addition, a cannula had also been inserted vertically at the usual co-ordinates at this site. In these circumstances intracaudate injection of picrotoxin caused myoclonus. The conclusion is that the phenomenon depends on (1) injection of picrotoxin (or other active agents) into the caudate nucleus, and (2) the presence of damage to the overlying sensorimotor cortex.

Electrophysiological investigations were in accord with this hypothesis. Following intracaudate injection of picrotoxin spikes first appeared in the injected striatum, then occurred synchronously also in the cortex co-incident with the clinical development of myoclonic jerks. McKenzie and Viik (1975) obtained similar results in cats. After infusion of d-tubocurarine into one caudate nucleus of the cat, spikes first appeared in that caudate, followed later by spikes in the ipsilateral motor cortex and then in both cortices. In our experiments and in those of MacKenzie and Viik (1975), spiking occurred rhythmically in relation to the myoclonic jerks, and was interrupted from time to time by short-lived bursts of more frequent repetitive discharges which correlated with the clonic focal motor seizures.

Initial uncertainty as to the source of the myoclonus was also the reason for investigating the effects of globus pallidus lesions on the myoclonus produced by intracaudate injection of picrotoxin, but the results were not clearcut. Electrolesions of moderate size confined to globus pallidus did not prevent the phenomenon, but the much larger lesions produced by electrocoagulation at two sites which destroyed globus pallidus did abolish the effect of a subsequent intracaudate injection of picrotoxin. Taken with the electrophysiological observations this suggests that the myoclonus originates in striatal discharges which are subsequently transmitted via the strio-pallidal outflow pathways. The large pallidal lesions, however, inevitably encroached into adjacent structures such as the internal capsule, which may have prevented transmission of descending activity from the cortex. Since the myoclonus appears to depend on abnormality in both caudate nucleus and sensorimotor cortex, it could result either from discharges in caudate transmitted via strio-pallidal outflow tracts and descending extrapyramidal pathways, or by discharges arising in the sensorimotor cortex (activated by the intracaudate picrotoxin injection) and transmitted via descending corticospinal pathways. Further experiments are required to decide on this matter.

Pharmacological Basis of the Myoclonus

Picrotoxin is a GABA antagonist (Precht and Yoshida, 1971; Hill, Simmonds and Straughan, 1973) although perhaps its actions are not entirely specific (Curtis and Johnston, 1974). Other agents that provoked myoclonus in our experiments were bicuculline, which is a more selective GABA antagonist (Curtis *et al.*, 1971), and benzylpenicillin which also possesses GABA antagonist activity (Curtis and Johnston, 1974). That d-tudocurarine, which caused the same phenomenon in McKenzie's and Viik's (1975) experiments, is a weak GABA antagonist (Curtis, Game and McCulloch, 1974) and has already been mentioned. Thus a range of more or less selective GABA antagonists provoked myoclonus when injected into the caudate nucleus. So, too, did dl-c-allylglycine which is an inhibitor of glutamic acid decarboxylase; the latency to onset of its effect was similar to its known delay in inhibiting the enzyme (Horton and Meldrum, 1973). McKenzie and Viik (1975) found that thiosemicarbazide provoked myoclonus in the rat: this drug also inhibits glutamic acid decarboxylase (Killam and Bain, 1957). Thus inhibiting GABA synthesis in the caudate nucleus caused myoclonus.

The myoclonus provoked by intracaudate injection of picrotoxin or dl-c-allylglycine could be stopped by subsequent intracaudate injection of GABA, or by dl-carnitine (γ-amino-β-hydroxybutyric acid) which acts as a GABA agonist. McKenzie and Viik (1975) found that glutamic acid, the amino acid precursor of GABA, also blocked d-tubocurarine-induced myoclonus. So increasing caudate GABA action stops the myoclonus provoked by intracaudate injection of GABA antagonists.

All the evidence points to the conclusion that blockade of GABA action in the caudate nucleus causes myoclonus. However, the data are not completely consistent. Intracaudate injections of GABA antagonists did not always cause myoclonus, neither did intracaudate injection of GABA and carnitine always stop picrotoxin or dl-c-allylglycine-induced myoclonus. This variation may have been due to the occasional misplaced injection (although the injection site was verified histologically in every animal) or to inadequate dosage, but, the effect of picrotoxin was not obviously dose-dependent. Indeed, it appears to be an all-or-none phenomenon; doses less than that required to produce jerks had no effect, while doses greater than this did not cause more intense myoclonus. This observation in itself is an unusual pharmacological phenomenon for a simple antagonist action. Despite these caveats the weight of evidence does implicate inhibition of GABA action in the caudate nucleus as the cause of the myoclonus.

The phenomena can also occasionally be produced by intracaudate injection of drugs believed to affect neurotransmitters other than GABA. Thus we have occasionally observed a similar myoclonus with intracaudate injections of apomorphine and carbachol. McKenzie and Viik (1975) also reported that intrastriatal carbachol could cause myoclonus. Such observations raise the possibility that the phenomenon may be non-specific, but this seems unlikely in view of all the other evidence. More probable is that manipulation of other transmitters in the caudate nucleus may, on occasion, indirectly cause inhibition of GABA action through intermediate neuronal pathways, or that these other drugs themselves block GABA activity in addition to their actions on other neurotransmitters.

Other experiments suggest that it is inhibition of GABA action in the caudate nucleus that is the critical stimulus to production of myoclonus, and that this occurs independently of activity of other neurotransmitter systems in the basal ganglia. Thus myoclonus provoked by intracaudate picrotoxin was not prevented by prior systemic treatment with drugs believed to block dopamine and noradrenaline receptors (chlorpromazine and haloperidol), nor by drugs which prevent storage (reserpine) or synthesis (α-methyl-p-tyrosine) of dopamine and noradrenaline. Neither did increasing or releasing cerebral dopamine and noradrenaline (L-dopa and amphetamine) affect the myoclonus. Drugs increasing cerebral 5-hydroxytryptamine (5-hydroxytryptophan) or blocking cerebral 5-hydroxytryptamine action (reserpine and methysergide) were also without effect. Reserpine did appear to enhance somewhat the myoclonus provoked by intracaudate picrotoxin. In view of the other data this seems unlikely to have been due to an effect on brain monoamines, but an alternative explanation is not apparent. Blockade of cholinergic action with scopolamine somewhat inhibited the myoclonus, but did not prevent it. This may suggest some cholinergic modulation of the phenomenon, but McKenzie and Viik (1975) found that physostigmine and acetylcholine had no effect on the myoclonus provoked by intrastriatal d-tubocurarine.

The overall conclusion is that myoclonus provoked by intracaudate picrotoxin (or other GABA antagonists) is not critically dependent on cerebral dopamine, noradrenaline, 5-hydroxytryptamine or acetylcholine systems. Since all these neurotransmitters are present in the basal ganglia, the tentative conclusion is that the GABA receptors in the caudate nucleus affected by picrotoxin lie distal or downstream to dopamine, noradrenaline, 5-hydroxytryptamine and acetylcholine neurons and pathways.

SUMMARY

Focal injections of drugs acting on GABA-mediated inhibitory mechanisms were made in various brain areas in unanæsthetized rats through chronically implanted steel guide cannulæ. Picrotoxin (0·5 – 1·5 μg in 2 μl saline) administered unilaterally into the caudate nucleus through a vertical guide which traversed the sensorimotor cortex induced a contralateral focal myoclonus (of the forelimb when the injection was anterior and the hindlimb when posterior), beginning after 6 min and lasting 52 min. EEG recording showed spikes appearing in the striatum preceding the myoclonic jerks, but subsequently occurring concurrently with the jerks. Comparable myoclonus was induced by allylglycine (100–150 μg), but the latency was longer (47 min) and so was the duration (65–200 min). Weaker myoclonus was seen after bicuculline (1–2 μg) or benzylpenicillin (1 unit). GABA (100–750 μg) injected after picrotoxin or allylglycine abolished myoclonus within 2 min. Picrotoxin (1 μg) administered into one caudate nucleus, using an angled guide which did not traverse the sensorimotor cortex, induced myoclonus only when the sensorimotor cortex had been damaged by a vertical guide cannula. Injections of picro-

toxin into the cortex overlying the caudate nucleus or into the thalamus did not produce focal myoclonus.

Systemic administration of drugs known to modify activity at central monoaminergic synapses such as 5-hydroxytryptophan, methysergide, α-methylparatyrosine, L-dopa plus carbidopa, chlorpromazine, haloperidol, clonidine and amphetamine, did not effect myoclonus induced by picrotoxin. Scopolamine 10 mg/kg delayed the onset of myoclonus and slowed its frequency. Reserpine increased the duration and frequency of myoclonus. Electrolytic lesions which destroyed the globus pallidus and some surrounding tissue prevented the appearance of myoclonus after intracaudate picrotoxin.

In this animal model, myoclonic jerks arise when cortical damage is combined with impairment of GABA-mediated inhibition in the caudate nucleus. A similar mechanism may be responsible for myoclonus in cerebral degenerative disorders in man.

REFERENCES

BIRD, E. D (1976) Biochemical studies on γ-aminobutyric acid metabolism in Huntington's chorea. In: *Biochemistry and Neurology*. Edited by H. F. Bradford and C. D. Marsden. London: Academic Press, pp. 83-92.

—— and IVERSEN, L. L. (1974) Huntington's chorea. Post-mortem measurement of glutamic acid decarboxylase, choline acetyltransferase and dopamine in basal ganglia. *Brain*, **97**, 457-472

—— MACKAY, A. V. P., RAYNER, C. N. and IVERSEN, L. L. (1973) Reduced glutamic acid decarboxylase activity of post-mortem brain in Huntington's chorea. *Lancet*, **i**, 1090-1092.

CURTIS, D. R., DUGGAN, A. W., FELIX, D., JOHNSTON, G. A. R. and MCLENNAN, H. (1971) Antagonism between bicuculline and GABA in the cat brain. *Brain Research, Amsterdam*, **33**, 57-73

—— GAME, C. J. A. and MCCULLOCH, R. M. (1974) Antagonism of inhibiting amino acid action by tubocurarine. *British Journal of Pharmacology*, **52**, 101-103.

—— and JOHNSTON, G. A. R. (1974) Amino acid transmitters in the mammalian central nervous system. *Ergebnisse der Physiologie Biologischenchemie und Experimentellen Pharmakologie*, **69**, 97-187.

HALL, R. D. and LINDHOLM, E. P. (1974) Organization of motor and somatosensory neocortex in the albino rat. *Brain Research, Amsterdam*, **66**, 23-38.

HILL, R. G., SIMMONDS, M. A. and STRAUGHAN, D. W. (1973) A comparative study of some convulsant substances as γ-aminobutyric acid antagonists in the feline cerebral cortex. *British Journal of Pharmacology*, **49**, 37-51.

HORTON, R. W. and MELDRUM, B. S. (1973) Seizures induced by allylglycine, 3-mercaptopropionic acid and 4-deoxypyridoxine in mice and photosensitive baboons, and different modes of inhibition of cerebral glutamic acid decarboxylase. *British Journal of Pharmacology*, **49**, 52-63

KILLAM, K. F. and BAIN, J. A. (1957) Convulsant hydrazides I: in vitro and in vivo inhibition of vitamin B_6 enzymes by convulsant hydrazides. *Journal of Pharmacology and Experimental Therapeutics*, **119**, 225-262.

König, J. F. R. and Klippel, R. A. (1963) *The Rat Brain*. Baltimore: Williams and Wilkins.

McGeer, P. L., McGeer, E. C. and Fibiger, H. C. (1973*a*) Glutamic acid decarboxylase and choline acetylase in Huntington's chorea and Parkinson's disease. *Lancet*, **ii**, 623–624.

—— —— —— (1973*b*) Choline acetylase and glutamic acid decarboxylase in Huntington's chorea. A preliminary study. *Neurology, Minneapolis*, **23**, 912–917.

McKenzie, G. M., Gordon, R. J. and Viik, K. (1972) Some biochemical and behavioural correlates of a possible animal model of human hyperkinetic syndromes. *Brain Research, Amsterdam*, **47**, 439–456.

—— and Viik, K. (1975) Chemically induced choreiform activity: Antagonisms by GABA and EEG patterns. *Experimental Neurology*, **46**, 229–243.

Marsden, C. D., Meldrum, B. S., Pycock, C. and Tarsy, D. (1975) Focal myoclonus produced by injection of picrotoxin into the caudate nucleus of the rat. *Journal of Physiology, London*, **246**, 96P.

Perry, T. L., Hansen, S. and Kloster, M. (1973) Huntington's chorea: deficiency of γ-aminobutyric acid in brain. *New England Journal of Medicine*, **288**, 337–342.

Precht, W. and Yoshida, M. (1971) Blockage of caudate-evoked inhibition of neurons in the substantia nigra by picrotoxin. *Brain Research, Amsterdam*, **32**, 229–233.

Pycock, C. J. (1976) Effects of blocking nigrostriatal γ-aminobutyric acid receptors. In: *Biochemistry and Neurology*. Edited by H. F. Bradford and C. D. Marsden. London: Academic Press, pp. 93–102.

—— Horton, R. W. and Marsden, C. D. (1976) The behavioural effects of manipulating GABA function in the globus pallidus. *Brain Research, Amsterdam*, **116**, 353–359.

(*Received August 2, 1977*)

Brain (1978), **101**, 163–185

WORD-COMPREHENSION AND WORD-RETRIEVAL IN PATIENTS WITH LOCALIZED CEREBRAL LESIONS

by A. K. COUGHLAN *and* ELIZABETH K. WARRINGTON

(*From the National Hospital, Queen Square, London WC1*)

INTRODUCTION

IMPAIRMENTS in word-comprehension and word-retrieval are common consequences of left hemisphere lesions, but the nature of these deficits and their anatomical correlates are by no means well established.

Word-comprehension disorders are commonly associated with damage to the left temporal lobe, particularly to Wernicke's area (Luria, 1973; Goodglass and Geschwind, 1976). Most of the evidence for this view, however, derives from clinical observation, single case reports (Yamadori and Albert, 1973) and the relatively poor word-comprehension of Wernicke's aphasics as compared with other types of aphasic patients (Goodglass, Klein, Carey and Jones, 1966; Goodglass, Gleason and Hyde, 1970) rather than from comparative studies of groups specifically selected according to site of lesion. The relationship between locus of lesion and naming disorders remains controversial. Some authors (Goldstein, 1948; Goodglass and Kaplan, 1972) consider that naming shows relatively little specificity to the site of lesion within the left hemisphere, whilst others (Symonds, 1953; Brain, 1961; Hécaen and Angelergues, 1964; Newcombe, Oldfield, Ratcliffe and Wingfield, 1971) emphasize temporal lobe damage.

Establishing anatomical correlates of word-comprehension and word-retrieval deficits is confounded by the probability that even these basic skills are multicomponent and therefore sustained by a number of different functional systems. Disruption in any of these systems may impair the skill and each system may have its own anatomical correlates. Thus whilst the investigation of the anatomical correlates of word-comprehension and word-retrieval skills themselves is of clinical interest, any correlations found should also be related to the underlying functional components. Although the systems sustaining word-comprehension and word-retrieval cannot be unequivocally specified it is reasonable to assume that they include phonemic, semantic and, in the case of word-retrieval, articulatory processes. Evidence for the discrete organization of these systems may be adduced from a variety of sources, including clinical observations on the nature of pure word-deafness (Goodglass and Geschwind, 1976), the types and distributions of errors in word-comprehension and word-retrieval yielded by aphasics (Schuell and Jenkins, 1961; Barton, Maruszewski and Urrea, 1969) and investigations by Warrington (1975) which have shown that some instances of word-comprehension and word-retrieval deficits may derive from the selective impairment of semantic memory—that system in which words are stored, related and retrieved—rather than from phonemic or articulatory disturbances. It is therefore the aim of this study to examine the nature of word-comprehension and word-retrieval deficits in patients with localized cerebral lesions and to consider relationships between site of lesion and functional deficits, particularly with regard to semantic memory.

SUBJECTS

The subjects were 57 patients with unilateral left hemisphere lesions (LH Group), 43 patients with unilateral right hemisphere lesions (RH Group) and 52 neurological control patients (Controls) with extra-cerebral lesions. Subjects were all native speakers of English and all the cerebral lesion subjects were right-handed. None of the subjects displayed peripheral deficits of vision, hearing or motor control of sufficient severity to impair performance on the test battery. The left hemisphere lesions comprised 52 tumours, 3 evacuated hæmatomas, one abscess and one gunshot wound; the right hemisphere lesions comprised 37 tumours, 3 evacuated hæmatomas, one abscess, one gunshot wound and one lobectomy for relief of epilepsy. The presence and site of lesion in the cerebral lesion patients were established from positive findings on at least two reliable neurological techniques (*viz* radio-active brain scan, angiography, air-encephalography or EMI scan) and/or surgeons' post-operative reports. Subjects were then classified into frontal, temporal, parietal and occipital localization subgroups within each hemisphere according to site of lesion. Lesions that straddled two lobes were classified into both appropriate subgroups, so the subgroups were not exclusively determined. The sites of lesions and the composition of the localization subgroups for the left and right hemisphere groups are given in Table 1. Although the patients formed a consecutive series and were selected only on the basis of having a unilateral lesion it was found that temporal lesions were relatively over-represented. There were sufficient patients with lesions involving other cerebral areas, however, to allow the performance of intra-hemisphere frontal, temporal and parietal subgroups to be compared. Tests were administered during two sessions of approximately one hour each. These two sessions were never more than three days apart and tests were randomly distributed between the sessions. The majority of subjects completed all the tests but occasional omissions occurred because of clinical considerations not of relevance to this investigation.

The presence of clinically apparent dysphasia in the cerebral lesion patients was judged from their abilities to describe a set of picture stories The same set of stories was used for each patient (including Controls). Thirty-four of the 57 left hemisphere subjects were considered to be dysphasic and dysphasia was suspected, but not regarded, as unequivocal, in a further 5. One of the 43 right hemisphere subjects was also found to be dysphasic.

All subjects were in the age range 21–70 years, there were no significant differences in age or number of years schooling between the Control, left hemisphere and right hemisphere groups, between the right hemisphere localization subgroups or between the left hemisphere localization subgroups. (Means and standard deviations for the Control, RH and LH Groups are given in Table 2). Inspection of the premorbid occupations of the subjects indicated that the various groups were satisfactorily matched in terms of the achievements/social status of their members

TABLE 1. DISTRIBUTION OF LESION SITES IN LH AND RH GROUPS AND ALLOTMENT OF PATIENTS TO LOCALIZATION GROUPS

Site of lesion	*No. in LH group*	*No. in RH group*
Frontal lobe	6	8
Temporal lobe	22	14
Parietal lobe	8	5
Fronto-temporal	4	4
Fronto-parietal	7	5
Temporo-parietal	7	2
Parieto-occipital	3	3
Temporo-parieto-occipital	—	1
Occipital lobe	—	1
Total	57	43
Total number of lobe sites affected	78	59

Localization groups	*No. in LH group*	*No. in RH group*
Frontal	17 (22%)	17 (29%)
Temporal	33 (42%)	21 (35%)
Parietal	25 (32%)	16 (27%)
Occipital	3 (4%)	5 (8%)
Total	78 (100%)	59 (100%)

TABLE 2. MEANS AND STANDARD DEVIATIONS FOR AGE AND SCHOOL-LEAVING AGE IN CONTROL, RH AND LH GROUPS

	Control (N = 52)	*RH* (N = 43)	*LH* (N = 57)
Age (yrs)	47·7 (12·7)	47·9 (13·6)	47·4 (12·7)
School-leaving age (yrs)	15·0 (1·5)	15·2 (1·4)	15·1 (1·5)

METHODS

Preliminary Tests

(1) *Current IQ.* A current level of intellectual functioning for each subject was derived from the subject's performance on the B and C sets of Raven's Progressive Matrices (Raven, 1958, 1960). Subjects were screened on items A5, A6 and A7 and given help with them if necessary. The B and C sets were then administered. It was observed in a pilot study that some subjects would make errors by going through the test rapidly and too casually. Consequently the first error made by any subject was greeted with the phrase 'Are you sure?' from the examiner. This appeared to make subjects concentrate adequately on the items. Scores from the B and C sets were extrapolated to give an estimated full score by reference to the expected patterns of scores as given in the Individual Test table in the matrices guidebook. If the

scores obtained in the B and C sets fell between two of the patterns in the table a weighted average of the nearest upper and lower full score estimates was taken.

The estimated matrices full scores were converted to equivalent full scale Wechsler-Bellevue IQs using a table prepared by Dr. H. R. Beech. This table was prepared by converting matrices scores for each age between 20 and 65 years to percentile rankings, and then converting the percentile rankings to standard deviation equivalents of Wechsler-Bellevue IQs and hence to actual Wechsler-Bellevue IQs. (H. R. Beech, personal communication).

(2) *Phoneme Discrimination.* Forty pairs of monosyllabic words were used. In 20 of the pairs the 2 words differed in either initial or final consonant, and the pairs were selected to range between easy and difficult phonemic discriminations. In the remaining 20 pairs the 2 words were identical. Subjects had to say or indicate whether the words in each pair were the same or different. The word-pairs were presented on tape, with about a one-second gap between the words in each pair and about seven seconds between successive pairs. Each pair was presented once only and the order of 'same' and 'different' pairs was randomized. Four examples of the task were given to each subject prior to testing. The test items and examples are given in the Appendix. Maximum score = 40 (Chance score = 20).

(3) *Articulation.* Subjects were asked to repeat the 32 monosyllabic words in the dyspraxia/dysarthria section of the Minnesota Test for the Differential Diagnosis of Aphasia (Schuell, 1965). Each word was presented once only. Repetitions were required to be correct first time, that is, spontaneous corrections by the subject were not credited. Maximum score = 32.

(4) *WAIS Vocabulary Subtest (Wechsler, 1955).* This test requires definitions of words of increasing difficulty. In order to keep in line with the other tests in this study the standard administration was modified and the words were presented orally only, that is, subjects were not permitted access to the written versions.

(5) *Modified Token Test.* This modified and shortened version of the De Renzi and Vignolo (1962) Token Test employed Weigl's blocks presented in a random array and consisted of 15 complex but abstract commands involving these blocks (for example, 'Put the red circle between the yellow triangle and the green triangle'). Commands were spoken, and presented once only. Scoring was pass or fail on each command. The test items are given in the Appendix. Maximum score = 15.

(6) *Modified Peabody.* This was a modification of the Peabody Picture Vocabulary Test (Dunn, 1959). The original test consists of 150 items ranging from very easy to very difficult items in which the subject is required to identify which of four pictures means the same as a given spoken word. Two equivalent forms of the original test, Form A and Form B, are available. The Modified Peabody of this study used 60 items only; these were items 42–101 of Form A with 4 of the items, Nos. 60, 72, 87 and 92, replaced by those from Form B. Repetition of the test item words were given if necessary, and subjects with severe visual field defects who tended to neglect one side of space were given assistance by the examiner pointing in turn to each of the four pictures for each item. Four examples of the task were given to each subject prior to testing. Maximum Score = 60 (Chance score = 15).

(7) *Auditory Choice vocabulary.* This test consisted of 60 word-comprehension items of the type 'Does X mean A or B?' in which the subject has to say or indicate which of the two alternatives has the same meaning as the word X. The test comprised two sections: in the first 30 items (Narrow choice) the A and B choices for each item were semantically related (for example, 'Does vacant mean empty or open?'), whereas in the second 30 items (Wide choice) the choices were semantically unrelated (for example, 'Does serene mean rope or calm?'); but as the use of these two separate sections did not prove useful (there was a ceiling effect on the wide choice list), this paper only reports the combined data of the two sections. The items were presented orally and repetitions were given if necessary. Four examples of the task (two for each section) were given to each subject prior to testing. The test items and the examples are given in the Appendix. Maximum score = 60 (Chance score = 30).

Word-comprehension and Word-retrieval Tests

(8) *Object Naming.* Subjects were presented with an array of 15 objects and asked to name each one when it was pointed to by the examiner. If the name for an object was not given correctly within five seconds the subject was regarded as having failed on that item. Subjects were allowed a further ten seconds, however, to produce the name on items on which they had failed, and all their responses occurring within the total of fifteen seconds allowed were recorded If the correct name was not given within this fifteen seconds the subject was presented with a choice of three names (the correct name and two semantically related distractors) and asked to select the correct one. The set of names was repeated if necessary. The objects' names and the sets of three choices for name-recognition are given in the Appendix. Maximum score, Object Naming = 15. Maximum score, Object Naming Recognition = 15 (Chance score = 5).

(9) *Description Naming.* Subjects were asked to name objects from verbal descriptions. The test comprised 15 items, each of which was presented once, orally. If the name for an object was not given correctly within seven seconds the subject was regarded as having failed on that item. Subjects were allowed a further eight seconds to produce the names on items on which they had failed, and all their responses occurring within the total of fifteen seconds allowed were recorded. If the correct name was not given within this fifteen seconds the description was repeated and then a choice of three names was presented (the correct name and two semantically related distractors) and the subject asked to select the correct one. The set of names was repeated if necessary. The descriptions, the objects they refer to, and the sets of three choices for name-recognition are given in the Appendix. Maximum score, Description Naming = 15. Maximum score, Description Naming Recognition = 15 (Chance score = 5).

ANALYSIS OF RESULTS

In order to examine the effects of laterality of lesion, comparisons have been made between the performances of Control, RH and LH Groups. The finding of substantial LH deficits in this study has led to investigation of the effects of localized left hemisphere lesions first by comparison of the performances of non-exclusive LH frontal, temporal and parietal groups and second by comparison of exclusive LH temporal and non-temporal groups (the latter consisting of all LH patients whose lesions do not involve the temporal lobe). Systematic investigation of the effects of localized right hemisphere lesions has not been warranted in view of the generally satisfactory performance of the RH Group. However, some instances of relatively minor RH deficits have been found, and in these cases the performances of RH frontal, temporal and parietal groups have been compared. All comparisons between groups have been carried out using the two-tailed Student's t-test. Because three t-tests are needed to compare three groups two at a time, results are not considered to be significant unless a confidence level of $P < 0{\cdot}02$ is reached. $P < 0{\cdot}05$ is regarded as a trend.

In order to examine the incidence of clear-cut deficits amongst the population with cerebral lesions, 'cut-off' scores, labelled C-2 and R-2 levels, were employed on each test. The C-2 level on a given test was approximately two standard deviations below the Control Group's mean score on that test and represented the level *at or below* which not more than 5 per cent of the Control subjects scored. Thus an individual displayed a test deficit if his/her score on a particular test fell *at or below* the C-2 cut-off level for that test. The C-2 levels were instituted to differentiate between the Control Group and subjects with brain lesions but because of the low incidence of deficits amongst the RH patients on some of the tests they were at times equally effective in differentiating LH subjects from RH subjects. However, on a number of the tests it was necessary to develop separate R-2 cut-off scores, *at or below* which not more than 5 per cent of the RH subjects scored, in order to discriminate between subjects in LH and RH Groups. The R-2 cut-off level on a given test was approximately two standard deviations below the RH Group's mean score.

The analysis of all the investigations are presented in the next section. The results of each test are discussed individually, but for economy of presentation the data are tabulated according to the groups being compared, that is, performance and t-test data for all tests for Control, RH and LH Groups (Table 3); performance and t-test data for all tests for LH frontal, temporal and parietal groups (Table 4); performance and t-test data for all tests for LH temporal and non-temporal groups (Table 5). The incidence of deficits in Control, RH and LH Groups and in LH temporal and non-temporal groups is given in Table 6. Finally, an analysis of the LH Group errors on the naming task is presented in Table 7.

Preliminary Tests

Current IQ. Both RH and LH Groups displayed a significantly lower mean IQ (as determined from Raven's Matrices) than that of the Control Group (Table 3). Within the left hemisphere there were no significant differences in IQ between frontal, temporal and parietal subgroups or between temporal and non-temporal subgroups (Tables 4 and 5). Within the right hemisphere the parietal group yielded the lowest mean IQ, but again no significant intra-hemisphere differences, or trends towards them, were found. Despite the significantly poor performances of the LH and RH Groups only a small percentage of subjects within each group (i.e. less than 20 per cent) displayed deficits at the C-2 level (Table 6). Similarly, only small percentages of subjects in the left hemisphere temporal and non-temporal groups fell below Control Group limits.

Phoneme Discrimination. Control, RH and LH Groups all scored at similar levels, as did the LH subgroups, but there was no ceiling effect on this test. There were no significant differences between the Control, RH and LH Groups or between the left hemisphere subgroups (Tables 3, 4 and 5). Only 3 of the 57 LH subjects displayed deficits at the C-2 level test (Table 6). Two of these 3 were capable of repeating monosyllables without difficulty suggesting that their failures on the Phoneme Discrimination task were due to factors other than auditory imperception.

Articulation. Although Control, RH and LH Groups all achieved very similar mean scores, the LH Group was significantly impaired compared with the Control Group (Table 3). The RH and LH Groups attained scores of 31·6 and 31·1 respectively, both being close to ceiling level. There were no significant differences

TABLE 3. MEANS AND STANDARD DEVIATIONS FOR CONTROL, RH AND LH GROUPS ON ALL TESTS, AND T-TEST DATA FOR COMPARISONS BETWEEN GROUPS

	Means (and standard deviations)			*t-values and significance levels*		
	Control (*N*=52)	*RH* (*N*=41–43)	*LH* (*N*=53–57)	*Control vs RH* (*df*=91–93)	*Control vs LH* (*df*=103–107)	*RH vs LH* (*df*=94–98)
Current IQ	112·4	101·5	104·1	3·96***	2·98**	0·86
	(12·4)	(14·4)	(16·1)			
Phoneme Discrimination	36·7	36·6	36·1	0·57	1·34	0·77
(Max. score = 40)	(2·5)	(2·6)	(3·7)			
Articulation	31·9	31·6	31·1	1·80	2·63**	1·56
(Max. score = 32)	(0·5)	(0·8)	(1·9)			
WAIS Vocabulary Subtest	11·8	11·3	8·9	1·08	4·85***	3·70***
(Age scaled)	(2·3)	(2·3)	(3·7)			
Modified Token Test	14·4	13·7	9·4	2·53*	6·63***	5·15***
(Max. score = 15)	(1·2)	(1·5)	(5·4)			
Modified Peabody	58·1	56·4	54·0	2·65**	4·31***	2·05^{t}
(Max. score = 60)	(1·9)	(4·1)	(6·4)			
Auditory Choice vocabulary	55·8	53·8	48·2	2·26^{t}	5·83***	3·83***
(Max. score = 60)	(3·9)	(4·9)	(8·8)			
Object Naming	14·7	14·7	11·0	0·26	5·77***	5·08***
(Max. score = 15)	(0·5)	(0·6)	(4·6)			
Description Naming	14·5	13·9	9·6	2·35^{t}	6·99***	5·41***
(Max. score = 15)	(0·8)	(1·4)	(4·9)			

t = trend, $P<0·05$, * = $P<0·02$; ** = $P<0·01$, *** = $P<0·001$

TABLE 4. MEANS AND STANDARD DEVIATIONS FOR LH FRONTAL, TEMPORAL AND PARIETAL SUBGROUPS ON ALL TESTS, AND T-TEST DATA FOR COMPARISONS BETWEEN SUBGROUPS

	Means (and standard deviations)			*t-values and significance levels*		
	Frontal (*N*=16–17)	*Temporal* (*N*=31–33)	*Parietal* (*N*=23–25)	*F vs P* (*df*=37–40)	*F vs T* (*df*=45–48)	*P vs T* (*df*=52–56)
Current IQ	109·6	104·7	100·4	1·89	1·03	1·01
	(14·9)	(16·4)	(15·9)			
Phoneme Discrimination	36·2	35·5	36·7	0·88	0·63	1·24
(Max. score = 40)	(1·3)	(4·5)	(2·2)			
Articulation	31·4	30·8	31·2	0·43	0·23	0·21
(Max. score = 32)	(1·2)	(2·4)	(1·3)			
WAIS Vocabulary Subtest	9·9	8·0	9·6	0·26	1·67	1·72
(Age scaled)	(3·9)	(3·7)	(3·2)			
Modified Token Test	10·8	8·7	9·1	1·13	1·33	0·30
(Max. score = 15)	(4·1)	(5·9)	(5·2)			
Modified Peabody	56·4	51·9	56·0	0·30	2·33^{t}	2·46*
(Max. score = 60)	(4·3)	(7·2)	(4·5)			
Auditory Choice Vocabulary	50·7	45·5	50·7	0·01	2·01	2·37^{t}
(Max. score = 60)	(8·0)	(8·8)	(7·4)			
Object Naming	13·4	9·7	11·7	1·58	2·96**	1·66
(Max. score = 15)	(1·8)	(4·8)	(4·0)			
Description Naming	11·9	7·9	10·7	1·01	2·94**	2·18^{t}
(Max. score = 15)	(2·7)	(5·2)	(4·2)			

t = trend, $P<0·05$, * = $P<0·02$, ** = $P<0·01$

TABLE 5. MEANS AND STANDARD DEVIATIONS FOR LH TEMPORAL AND NON-TEMPORAL SUBGROUPS ON ALL TESTS, AND T-TEST DATA FOR COMPARISONS BETWEEN THESE SUBGROUPS

	Means (and standard deviations)		*t-values and levels of significance*
	Temporal ($N=31$–33)	*Non-temporal ($N=23$–24)*	*T vs non-T ($df=52$–55)*
Current IQ	104·7 (16·4)	103·1 (15·2)	0·44
Phoneme discrimination (Max. score = 40)	35·5 (4·5)	37·1 (1·7)	1·63
Articulation (Max. score = 32)	30·8 (2·4)	31·7 (0·5)	1·82
WAIS Vocabulary Subtest (Age scaled)	8·0 (3·7)	10·1 (3·4)	2·18^{t}
Modified Token Test (Max. score = 15)	8·7 (5·9)	10·4 (4·1)	1·20
Modified Peabody (Max. score = 60)	51·9 (7·2)	57·0 (3·1)	3·26**
Auditory Choice Vocabulary (Max. score = 60)	45·5 (8·8)	51·9 (7·0)	2·96**
Object Naming (Max. score = 15)	9·6 (4·8)	12·9 (3·1)	2·82**
Description Naming (Max. score = 15)	7·9 (5·2)	12·2 (3·1)	3 56***

t = trend, $P<0·05$. ** = $P<0·01$. *** = $P<0·001$.

between the left hemisphere frontal, temporal and parietal subgroups, or between temporal and non-temporal subgroups (Tables 4 and 5). Only 14 per cent of the LH subjects displayed deficits at the C-2 cut-off level (Table 6). It was also noted that on other tests requiring expression (for instance, the WAIS vocabulary subtest and description of a set of picture stories) only two of the LH subjects displayed articulatory difficulties of sufficient severity to impede their performance, and even in these patients such difficulties were relatively mild compared with other aspects of dysphasia. The incidence of deficits on the Articulation test was greater in the temporal group than in the non-temporal group but still very small compared with the incidence of deficits on other expressive tests (Table 6).

WAIS Vocabulary Subtest. The LH Group was significantly impaired compared with both the Control and RH Groups (Table 3). There were no significant differences in the performances of the left hemisphere frontal, temporal and parietal subgroups (Table 4), but there was a trend towards significant temporal inferiority in a temporal *vs* non-temporal comparison (Table 5). A moderate proportion of the LH subjects (i.e. 30 per cent) could be discriminated from the Control and

TABLE 6. CUT-OFF SCORE DATA: INCIDENCE OF DEFICITS IN CONTROL, RH AND LH GROUPS AND IN LEFT HEMISPHERE TEMPORAL AND NON-TEMPORAL GROUPS

					Left hemisphere subgroups	
	Cut-off	*Controls* ($N=52$)	*RH* ($N=41$–43)	*LH* ($N=53$–57)	*Temporal* ($N=31$–33)	*Non-temporal* ($N=22$–24)
Current IQ	C-2 = 87	2	5 (12%)	9 (16%)	6 (18%)	3 (13%)
	R-2 = 73	0	0	0	0	0
Phoneme Discrimination	C-2 = 31/40	2	1	3	3 (10%)	0
Articulation	C-2 = 30/32	0	4 (9%)	8 (14%)	7 (21%)	1
	R-2 = 29/30	0	0	5 (9%)	5 (15%)	0
WAIS Vocabulary (age-scaled)	C-2 = 7	1	2	17 (30%)	13 (39%)	4 (17%)
Modified Token Test	C-2 = 12/15	2	5 (12%)	33 (59%)	19 (58%)	14 (60%)
	R-2 = 9/15	1	1	24 (43%)	17 (52%)	7 (30%)
Modified Peabody	C-2 = 52/60	2	7 (16%)	14 (25%)	12 (36%)	2 (9%)
	R-2 = 45/60	0	1	7 (12%)	6 (18%)	1
Auditory Choice Vocabulary	C-2 = 45/60	2	4 (9%)	22 (39%)	17 (52%)	5 (22%)
	R-2 = 43/60	0	2	16 (28%)	12 (36%)	4 (17%)
Object Naming	C-2 = 13/15	1	2	32 (57%)	23 (70%)	9 (40%)
Description Naming	C-2 = 12/15	1	5 (12%)	29 (52%)	22 (67%)	7 (30%)
	R-2 = 11/15	0	2	28 (50%)	22 (67%)	6 (26%)

Percentages only quoted if greater than 5 per cent

RH Groups at the C-2 cut-off level (Table 6). Within the left hemisphere, deficits were more prominent in the temporal group than in the non-temporal group.

Modified Token Test. The LH Group was significantly inferior to both the Control and RH Groups, and the RH Group was mildly, but significantly inferior to the Control Group (Table 3). Within the left hemisphere there were no significant differences between the frontal, temporal and parietal subgroups or between the temporal and non-temporal subgroups (Tables 4 and 5). In view of the significant RH deficit on this task comparisons were also carried out between RH frontal, temporal and parietal subgroups, but no significant intra-right hemisphere differences were found. Substantial proportions of LH subjects (more than 40 per cent) could be discriminated from the Control and RH populations by the use of the C-2 and R-2 cut-off scores (Table 6). The left hemisphere temporal and non-temporal subgroups displayed an equally high incidence of deficits.

Word-comprehension and Word-retrieval Tests

Modified Peabody. The LH Group was significantly impaired compared with the Control Group and showed a trend towards being significantly inferior to the RH Group. A more pronounced LH *vs* RH difference was precluded by significant RH impairment on this task on comparison of the RH Group with the Control Group (Table 3). Comparisons between the left hemisphere frontal, temporal and parietal subgroups revealed that the temporal group was significantly impaired compared to the parietal group and showed a trend towards being significantly inferior to the frontal group (Table 4). A temporal *vs* non-temporal comparison also revealed a significant temporal impairment (Table 5). In view of the significant

RH deficit on this task comparisons were also carried out between RH frontal, temporal and parietal groups, but no significant intra-right hemisphere differences were found. Twenty-five per cent of the LH subjects displayed deficits at or below the C-2 level on this test, and within the left hemisphere the incidence of deficits was much greater in the temporal than in the non-temporal group (Table 6).

Auditory Choice Vocabulary. The LH Group was significantly inferior to both the Control and RH Groups. There was also a trend towards significant impairment of the RH Group compared with the Control Group (Table 3). Within the left hemisphere the temporal group scored lower than either the frontal or parietal groups and there was a trend towards significant temporal inferiority compared with the parietal group (Table 4). A temporal *vs* non-temporal comparison revealed a significant temporal impairment (Table 5). Moderate proportions of LH subjects (about 30 per cent) could be discriminated from the Control and RH subjects by use of the C-2 and R-2 cut-off scores (Table 6). There was a much greater incidence of deficits in the temporal group than in the non-temporal group. The vast majority of LH subjects who displayed deficits on the auditory choice vocabulary task also displayed deficits on the Modified Peabody and *vice versa*, and there was a significant association of deficits at the C-2 level on each task. ($\chi^2 = 25{\cdot}55$, $P < 0{\cdot}001$). Thus, in the majority of instances of word-comprehension impairment, deficits occurred concurrently on auditory-visual and auditory-auditory matching tasks.

Object Naming. The LH Group was significantly impaired compared with both Control and RH Groups (Table 3). Within the left hemisphere the temporal group scored lower than either the frontal or parietal group and was significantly impaired compared with the frontal group (Table 4). Significant temporal group impairment was revealed in a temporal *vs* non-temporal comparison (Table 5). A substantial proportion of LH subjects (i.e. 57 per cent) could be discriminated from the Control and RH subjects by use of the C-2 cut-off score (Table 6). Although the incidence of Object Naming deficits amongst the LH subjects was much greater in the temporal group than in the non-temporal group there was none the less a sizeable incidence of deficits within the non-temporal group. However, further examination of the data indicated that the naming deficits arising from non-temporal lesions are generally milder than those which arise from temporal damage. Adopting a stringent cut-off score of *8 or less* correct out of 15 on Object Naming, 14 LH patients still displayed a deficit, but of these, 13 (93 per cent) had temporal lesions or lesions involving the temporal lobe. Severe Object Naming deficits would therefore seem to be good indicators of temporal damage.

Description Naming. The LH Group was significantly impaired compared with both the Control and RH Groups. There was also a trend towards significant impairment of the RH Group compared with Controls (Table 3). Within the left hemisphere the temporal group was significantly inferior to the frontal group and showed a trend towards being significantly inferior to the parietal group (Table 4).

Significant temporal group impairment also emerged in a temporal *vs* non-temporal comparison (Table 4). Substantial proportions of LH subjects (about 50 per cent) could be discriminated from Control and RH subjects by means of the C-2 and R-2 cut-off scores (Table 6). Although there was a moderate incidence of deficits in the left hemisphere non-temporal group, the incidence was far greater in the temporal group.

The vast majority of LH subjects who displayed deficits on Description Naming also displayed deficits on Object Naming and *vice versa*, that is, deficits occurred concurrently on auditory-visual and auditory-auditory naming tasks. The association of deficits at the C-2 level on each task was significant at the level $(P < 0{\cdot}01$ $(\chi^2 = 23{\cdot}28)$.

Error Analysis. The naming errors made by the LH subjects on the Object Naming and Description Naming tasks were classified into the following types:

Delayed correct	—Correct response produced after naming failure has been recorded, i.e. response occurring between 6″–15″ for Object Naming and 8″–15″ for Description Naming.
No response	—No verbal response within 15″.
Semantic	—Semantically associated word.
Descriptive	—Phrase indicating knowledge of additional properties of the object or of its use or function.
Random word	—Word unrelated to the object name.
Articulatory	—Incompletely articulated attempt to name.
Literal paraphasic	—Word related in sound to the object name, including sound-related neologisms.
Neologistic	—Random nonsense word with no obvious relation to object name.
Random verbalization	—Random phrases or comments (including neologistic phrases).
Perseverative	—Responses from preceding test items.

Table 7 shows the results of this error analysis for the 56 LH subjects tested on the naming tasks. On Object Naming the most common errors were no-response and descriptive, which occurred with equal frequency. On Description Naming no-response errors were by far the most frequent, with semantic errors second. Of note were the low frequencies of articulatory, literal paraphasic and neologistic errors on each test, indicating that impairments at executive and/or phonetic levels were only relatively minor causes of naming difficulty. This latter observation accords well with the findings of only minor articulatory and auditory-perceptual disturbances amongst LH subjects on other tests, for example, Articulation and Phoneme Discrimination.

In that naming does not appear to have been seriously disrupted by articulatory and phonetic impairments it seems reasonable to attribute delayed-correct, no-response, descriptive and semantic errors to either deficits in the word-store or to deficits in retrieval from it. Such errors account for about 75 per cent of the total errors on each test. Only 9 per cent of the total errors on each test are attributable to mis-articulations, literal paraphasias and neologisms (i.e. executive and phonetic disturbances). The remaining 17 per cent are made up of random words, random verbalizations and preservative errors, and are probably more appropriately regarded as intrusions rather than failures in processes directly involved in naming.

TABLE 7. CLASSIFICATION OF NAMING ERRORS MADE BY LH SUBJECTS

	Object Naming	*Description Naming*
Total no. of naming failures made by 56 LH subjects	224	302
Types of error		
Delayed correct	27 (11%)	19 (6%)
No response	55 (23%)	143 (45%)
Semantic	29 (12%)	59 (19%)
Descriptive	57 (24%)	19 (6%)
Random word	19 (8%)	11 (4%)
Articulatory	11 (5%)	13 (4%)
Literal paraphasic	3 (1%)	5 (2%)
Neologistic	6 (3%)	9 (3%)
Random verbalization	20 (9%)	31 (10%)
Perseverative	9 (4%)	3 (1%)
Total of types of error	236* (100%)	312* (100%)

* Total number of types of error exceeds total number of naming failures as very occasionally two types of error were made on one item.

In order to assess the effects of word-store disturbances on naming, the name-recognition abilities of the LH patients were also investigated (*see* Method—Tests 8 and 9). On Object Naming 14 LH subjects (25 per cent) made errors of name recognition, and on Description Naming 17 LH subjects (30 per cent) made name recognition errors. Eleven of the subjects who made such recognition errors made them on both tests, demonstrating a significant association between performances on auditory-visual and auditory-auditory matching tasks ($\chi^2 = 17{\cdot}60$, $P < 0{\cdot}001$). The Object Naming scores of the 14 subjects making recognition errors ranged between 0/15–14/15 correct (mean, 6·6/15); the Description Naming scores of the 17 subjects who made recognition errors also ranged between 0/15–14/15 correct (mean, 4·3/15). On Object Naming the 14 patients who made recognition errors made 34 such errors, numerically equivalent to 31 per cent of their naming failures. If, as is possible, the recognition errors represent only two-thirds of the true number of recognition failures (one-third being guessed correctly in a three-choice task) then the true number of recognition failures is likely to be *c.* 50 and numerically equivalent to almost half of these subjects' naming failures.

As with naming deficits, name recognition errors would appear to be predominantly associated with temporal lesions. On Object Naming Recognition, 33 per cent of the temporal group patients (11) made errors as compared with 13 per cent of the non-temporal group patients (3). On Description Naming Recognition, 45 per cent of the temporal group patients (15) made errors as compared with only 9 per cent of the non-temporal group patients (2).

DISCUSSION

This study is concerned with the effects of unilateral cerebral lesions on a variety of language skills, particularly on the skills of word-comprehension and word-retrieval. It will be argued that deficits in word-comprehension and word-retrieval in the series of patients investigated here are attributable to impairment of semantic memory processes, and that such impairment is specifically associated with left temporal lobe damage.

Three main groups of patients were tested—patients with unilateral left hemisphere lesions (LH Group), patients with unilateral right hemisphere lesions (RH Group) and a Control Group of neurological patients with miscellaneous extracerebral lesions (Controls). The vast majority of the lesions in the LH and RH Groups were tumours. One of the 43 RH patients (2 per cent) and 34 of the 57 LH patients (60 per cent) displayed clinically apparent dysphasia.

The LH Group was found to be significantly impaired compared with both Control and RH Groups on complex tasks of language comprehension and expression—*viz* in carrying out complex instructions on a modified version of the De Renzi and Vignolo (1962) Token Test and in defining the words on the WAIS Vocabulary Subtest (Wechsler, 1955). Highly significant LH impairments were also found on tasks of word-retrieval, Object Naming and Description Naming, and on tasks of word-comprehension, a modified version of the Dunn (1959) Peabody Picture Vocabulary Test and an Auditory Choice Vocabulary test.

In addition to the statistical demonstration of the LH Group's inferiority, substantial numbers of LH patients scored below the normal range of these various tests and could be clearly distinguished from Control and RH patients by means of 'cut-off' scores. These deficits cannot be ascribed to a reduction in general intellectual abilities in the LH Group, for although the LH Group displayed a significantly inferior mean IQ to that of the Control Group, that of the RH Group was even lower. A small number of LH subjects displayed IQs below the Control Group's range, but not all of these displayed deficits on the language tests just described. The vast majority of LH patients with clear-cut language deficits had IQs within the Control Group's range.

In contrast to the poor performance on other language tests only a few LH subjects scored below normal limits on tests of Phoneme Discrimination and

Articulation (the latter being a subtest from the Minnesota Test for the Differential Diagnosis of Aphasia, Schuell, 1965). No significant LH impairment was discernible on Phoneme Discrimination; Control, RH and LH Groups all scored at closely similar levels. On the Articulation test (repetition of monosyllabic words) it was found that although the LH Group mean score was significantly inferior to that of the Control group the majority of LH patients scored at ceiling level. Only a small percentage of LH patients displayed deficits on this test despite very strict scoring (spontaneous corrections were not credited). On other expressive tests (for example, description of picture stories and WAIS Vocabulary) only 2 of the 57 LH patients exhibited articulatory difficulties of sufficient severity to discernibly impair their performance and even in these cases the articulatory deficits were relatively mild compared with other aspects of dysphasia. Consequently the degree of articulatory impairment amongst the LH patients can be regarded as minimal.

These observations indicate that the word-comprehension and word-retrieval deficits of the LH group cannot be attributed to disruptions at the relatively peripheral input and output levels of phoneme discrimination and articulation. It therefore seems most likely that the word-comprehension deficits assessed in this study reflect disturbances in the word-store, that is, semantic memory, and that the word-retrieval deficits also reflect disturbances of this store or retrieval from it, that is, semantic retrieval. As regards the word-retrieval deficits, these conclusions are supported by an analysis of the types of error made on the naming tasks. Errors likely to reflect disruption of articulation or phonemic organization (articulatory, literal paraphasic and neologistic errors) accounted for only 9 per cent of the total errors on each test, whilst errors likely to reflect deficits in the word store or retrieval from it (no response, delayed correct, descriptive and semantic errors) accounted for about 75 per cent of the errors on each test. Although it is not possible to specify precisely the relative contributions of store and retrieval deficits in this latter 75 per cent of errors, an indication of the influence of store deficits on naming may be gained from the incidence of name recognition errors on the naming tasks. Such errors, which are further instances of word-comprehension deficits, were made by about half of the LH patients who displayed naming deficits, particularly those with the more severe naming impairments. Thus it appears that whilst semantic retrieval difficulties can account for the majority of naming failures amongst LH patients, semantic store deficits may none the less make substantial contributions in many cases. Whilst the conclusion reached in this study, therefore, is that the word-comprehension and word-retrieval deficits of the LH Group are predominantly attributable to impairment in semantic systems it is of note that Geschwind (1965, 1967) has ascribed some instances of naming and name-recognition failures in cross-modal naming tasks to disconnections between sensory systems and the speech area. The findings of this present study were that word-comprehension, name-recognition and naming impairments usually occur in both auditory-auditory as well as auditory-visual tasks, indicating that these impairments cannot appropriately be described in terms of disconnection syndromes and strengthening the view that they indeed represent semantic deficits.

Within the LH Group there was a surprisingly high incidence of patients with temporal damage considering that the patients formed a consecutive series selected only on the criterion of having a demonstrable left hemisphere lesion. Why temporal lesions should be over-represented is not clear. Nevertheless, there were sufficient patients with lesions in other regions of the left hemisphere to allow comparison of frontal, temporal and parietal groups (with some overlap in composition) and temporal and non-temporal groups (with no overlap in composition). The temporal subgroup generally fared worse on language tasks than other localization subgroups both in terms of incidence and severity of deficits, but it is of note that no significant effect of temporal lesions could be detected on the tasks of Phoneme Discrimination, Articulation and the Modified Token Test, and only a trend towards a significant deficit emerged on the WAIS vocabulary subtest. In contrast, significant temporal lobe deficits were obtained on word-comprehension and word-retrieval tasks.

Given the lack of impairment amongst the LH Group as a whole on the Phoneme Discrimination and Articulation tests it was not unexpected that no effects of localization would emerge on these tasks. As regards phoneme discrimination, however, Luria (1958, 1973) has asserted that such impairment is a common consequence of lesions of the posterior-superior aspect of the temporal lobe (Wernicke's area) and the underlying basis of Wernicke's dysphasia, whilst Blumstein, Baker and Goodglass (1977) have reported that Wernicke's dysphasics show little phonemic discrimination disturbance. The lack of phoneme discrimination impairment in this present study cannot be ascribed to a general lack of dysphasic symptomology, for, as noted earlier, massive LH deficits have been obtained on several other language tasks. Thus, in this study where the groups were determined according to site of lesion rather than to type of dysphasia, the finding that there is no substantial phoneme discrimination impairment in the temporal group strongly supports the position of Blumstein, Baker and Goodglass. The lack of significant temporal lobe impairments on the WAIS Vocabulary Subtest and the Modified Token Test, despite strong overall LH impairments on these tasks, affords two points. First, that performance on complex tests of language ability is sensitive to damage anywhere within the left hemisphere and secondly, that the significant effects of temporal lesions on naming and word-comprehension are selective, and not merely the consequence of an over-representation of temporal lesions within the LH Group. The specific association of temporal structures with word-comprehension has previously been implied by the relatively poor performance of Wernicke's dysphasics with respect to other dysphasic types on word-comprehension tasks (Goodglass *et al.*, 1966; Goodglass, Gleason and Hyde, 1970) and this present study substantiates this impression. Naming difficulties have been regarded as specifically associated with left temporal damage by a number of authors (Symonds, 1953; Brain, 1961; Hécaen and Angelergues, 1964) whilst others (e.g. Goldstein, 1948; Goodglass and Kaplan, 1972) consider them to be of little localizing significance. Although substantial proportions of patients in the frontal and parietal groups in this study displayed naming deficits, such deficits were more common and generally more severe in the temporal group. The most severe naming disorders (as exemplified by a score of 8 or less out of 15 on Object Naming and displayed by 14 of the LH patients) were almost exclusively the result of temporal lesions or lesions involving the temporal lobe. A similar observation has also been reported by Newcombe *et al.* (1971) in a study of the picture-naming deficits of men with focal missile wounds.

It has already been argued that both the word-comprehension and word-retrieval impairments of the LH patients in this present study may represent semantic deficits. The lack of phonemic or articulatory impairments amongst the patients with lesions of the left temporal lobe in this study, and the observation that both word-comprehension and word-retrieval deficits occur on both auditory-auditory and auditory-visual tasks, indicate that this notion applies equally strongly to the significant left temporal impairments found in word-comprehension and word-retrieval in this study. It would therefore appear that damage to temporal structures results in deficits in semantic memory and semantic retrieval to a much greater extent than does damage elsewhere in the left hemisphere.

In considering the effect of cerebral lesions on language skills we have so far been concerned with lesions of the left hemisphere. However, it deserves mention that some instances of impairment following lesions of the right hemisphere were also observed. Although the degree of impairment was invariably much less than that of the LH Group, significant RH deficits were found on the Modified Peabody and on the Modified Token Test, and trends towards significant deficits on Auditory Choice Vocabulary and Description Naming. In contrast, no signs of RH impairment were discernible on Phoneme Discrimination, Articulation, WAIS Vocabulary and Object Naming tasks. Swisher and Sarno (1969) have previously reported impaired Token Test performance following lesions of the right hemisphere and considered that this may reflect either inefficient scanning of the stimulus array or a high level linguistic deficit. Lesser (1974) has found significant right hemisphere deficits on picture vocabulary tasks despite adequate performance on other language tests involving pictorial material and thus concluded that lesions of the right hemisphere may specifically affect semantic comprehension. Although the tasks in this present study on which the RH Group did poorly all require some comprehension of word meanings it seems unlikely that this was the basis of their difficulty. First, no RH impairment was manifested in the WAIS vocabulary subtest, a test on which there were clearcut left hemisphere deficits. In addition, the Modified Token Test, one of the two tests to yield a significant RH deficit, requires only very limited appreciation of vocabulary. It also seems unlikely that poor RH performance can be attributed to minimal left hemisphere disturbance via an unsuspected degree of bilateral dysfunction as no RH deficit emerged on Object Naming, one of the most sensitive tests of LH damage. Perhaps the most plausible explanation of the pattern of RH performance is that it reflects difficulty in operating adequate (but as yet undefined) response strategies, that is, a high level cognitive deficit rather than an impairment in specific linguistic functions.

Finally, having attempted to establish and interpret some of the language deficits arising as a consequence of cerebral tumours it is appropriate to consider the clinical relevance of this study. Several of the tests employed have yielded 'cut-off' scores which may be used to differentiate subjects with brain lesions from the Control Group or subjects with left hemisphere lesions from Control subjects and subjects with right hemisphere lesions (*see* Table 6 and Appendix). It is hoped that clinicians may find these data useful in the detection and description of their patients' speech disorders. As regards interpretation, however, it must be emphasized that the semantic basis for word-retrieval and word-comprehension disorders revealed in this study may not be so predominant in other series of patients in which temporal lesions may be less well represented. The lesions of this series of patients were predominantly tumours and therefore liable to early detection and intervention; consequently the language deficits of these patients, although substantial, were likely to be less severe than those encountered in traumatic cases such as cerebrovascular accidents and missile wounds. There may well be greater sensory or articulatory components in the word-retrieval and word-comprehension deficits arising from traumatic ætiologies and it is possible that other aspects of language function not examined in this study, for example, syntax, are also sensitive to ætiology. Some tentative support for these suggestions comes from the observation that the patients in this series could not easily be classified into the conventional categories of Broca's and Wernicke's dysphasias—indeed, despite adequate representation of patients with anterior lesions, only one displayed a classical agrammatic Broca's dysphasia. Although examples of the fluent, paraphasic speech of Wernicke's dysphasia were found, the most noticeable feature of the expressive speech of the majority of the dysphasics in the study was anomia. Whether the qualitative differences which appear to be emerging between different populations are merely attributable to differences in severity of symptoms or whether they reflect crucial differences in the distributions of lesions occurring in these populations remains to be determined.

SUMMARY

Fifty-seven patients with unilateral left hemisphere lesions, 43 patients with unilateral right hemisphere lesions and 52 neurological control patients with extra-cerebral lesions were assessed on a battery of verbal tests designed to investigate word-comprehension and word-retrieval. The left hemisphere group was significantly impaired on most tests and some mild impairment was found in the

right hemisphere group. Many of the tests yielded 'cut-off' scores which could be effectively used to discriminate between the Control Group and patients with brain lesions, and between left and right hemisphere lesions. Deficits in word-comprehension and word-retrieval in the left hemisphere group could not be attributed to impairments in auditory-perceptual or articulatory processes and were considered to possibly reflect impairments in semantic memory and semantic retrieval. Patients in the left hemisphere Group with temporal lesions or lesions involving the temporal lobe were significantly more impaired on word-comprehension and word-retrieval tasks than patients with lesions in other regions of the left hemisphere, indicating an association between left temporal damage and semantic deficits.

ACKNOWLEDGEMENTS

We wish to thank the Physicians and Surgeons of the National Hospital for permission to study and report our findings on patients under their care.

REFERENCES

BARTON, M., MARUSZEWSKI, M. and URREA, O. (1969) Variation on stimulus context and its effect on word-finding ability in aphasics. *Cortex*, **5**, 351-365.

BLUMSTEIN, S. E., BAKER, E. and GOODGLASS, H. (1977) Phonological factors in auditory comprehension in aphasia. *Neuropsychologia*, **15**, 19-30.

BRAIN, W. R. (1961) *Speech Disorders · Aphasia, Apraxia and Agnosia.* London: Butterworth.

DE RENZI, E. and VIGNOLO, L. A. (1962) The Token Test: a sensitive test to detect receptive disturbances in aphasics. *Brain*, **85**, 665-678.

DUNN, L. M. (1959) *Peabody Picture Vocabulary Test.* Minnesota: American Guidance Service.

GESCHWIND, N. (1965) Disconnection syndromes in animals and man. *Brain*, **88**, 237-294.

—— (1967) The varieties of naming errors. *Cortex*, **3**, 97-112.

GOLDSTEIN, K. (1948) *Language and Language Disturbances.* New York: Grune and Stratton.

GOODGLASS, H. and GESCHWIND, N. (1976) Language disorders (aphasia). In: *Handbook of Perception.* Vol. 7. *Language.* Edited by E. C. Cartarette and M. P. Friedman. New York: Academic Press.

—— GLEASON, J. B. and HYDE, M. R. (1970) Some dimensions of auditory language comprehension in aphasia. *Journal of Speech and Hearing Research*, **13**, 595-606.

—— and KAPLAN, E. (1972) *The Assessment of Aphasia and Related Disorders.* Philadelphia: Lea and Febiger.

—— KLEIN, B., CAREY, P. and JONES, K. J. (1966) Specific semantic word categories in aphasia. *Cortex*, **2**, 74-89.

HÉCAEN, H. and ANGELERGUES, R. (1964) Localization of symptoms in aphasia. In: *Disorders of Language.* Edited by A. V. S. De Reuck and M. O'Connor. London: Churchill.

LESSER, R. (1974) Verbal comprehension in aphasia: an English version of three Italian tests. *Cortex*, **10**, 247-263.

LURIA, A. R. (1958) Brain disorders and language analysis. *Language and Speech*, **1**, 14–34.

—— (1973) *The Working Brain*. London: Allen Lane The Penguin Press.

NEWCOMBE, F., OLDFIELD, R., RATCLIFFE, G. and WINGFIELD, A. (1971) Recognition and naming of object drawings by men with focal brain wounds. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 329–340.

RAVEN, J. C. (1958) *Standard Progressive Matrices*. London: H. K. Lewis.

—— (1960) *Guide to the Standard Progressive Matrices*. London: H. K. Lewis.

SCHUELL, H. (1965) *The Minnesota Test for Differential Diagnosis of Aphasia*. Minneapolis: University of Minnesota Press.

—— and JENKINS, J. J. (1961) Reduction of vocabulary in aphasia. *Brain*, **84**, 243–261.

SWISHER, L. P. and SARNO, M. T. (1969) Token test scores of three matched patient groups. *Cortex*, **5**, 264–273.

SYMONDS, C. (1953) Aphasia. *Journal of Neurology, Neurosurgery and Psychiatry*, **16**, 1–6.

WARRINGTON, E. K. (1975) The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology*, **27**, 635–657.

WECHSLER, D. (1955) *Wechsler Adult Intelligence Scale Manual*. New York: Psychological Corporation.

YAMADORI, A. and ALBERT, M. L. (1973) Word category aphasia. *Cortex*, **9**, 112–125.

(*Received July 7, 1977*)

APPENDIX

Phoneme Discrimination (*Test No. 2*)

Examples:	top	top	(S)*
	day	say	(D)**
	green	greet	(D)
	big	big	(S)

type	type	(S)	king	king	(S)
sell	sell	(S)	leaf	leave	(D)
choke	joke	(D)	date	date	(S)
gale	tale	(D)	shock	shock	(S)
nod	nod	(S)	mine	mine	(S)
leg	led	(D)	rub	rum	(D)
sue	zoo	(D)	thigh	sigh	(D)
keen	keen	(S)	tune	tune	(S)
load	load	(S)	vote	note	(D)
than	van	(D)	seem	seen	(D)
meet	meet	(S)	talk	talk	(S)
rich	rip	(D)	both	both	(S)

part	path	(D)	bar	jar	(D)
sight	might	(D)	rough	rush	(D)
thin	thin	(S)	jam	jam	(S)
bake	bathe	(D)	shoot	boot	(D)
pat	cat	(D)	kite	kite	(S)
juice	juice	(S)	town	down	(D)
song	sock	(D)	teeth	teeth	(S)
fill	fill	(S)	loud	loud	(S)
			Score (ex 40)		

* S = same. ** D = different.

Modified Token Test (*Test No. 5*)

Using Weigl's Blocks in Random Array

1. Put the red circle on the green triangle.
2. Put the blue square behind the yellow circle.
3. Touch the blue circle with the red triangle.
4. Pick up the blue circle OR the red triangle.
5. Put the green square away from the yellow square.
6. If there is a black circle, pick up the red triangle. (Note. There is no black circle).
7. When I touch the green circle, you take the green square. (Note. Wait a few seconds before touching the green circle).
8. Put the green square beside the red circle.
9. Touch the squares, slowly and the circles, quickly.
10. Put the red circle between the yellow triangle and the green triangle.
11. Except for the green one, touch the circles.
12. Instead of the blue square, take the yellow circle.
13. Together with the yellow circle, take the blue circle.
14. After picking up the green square, touch the red circle.
15. Before touching the yellow circle, pick up the red square.

Scoring notes

Item No. 2: 'Behind' may be interpreted either with respect to the patient or the examiner (if facing the patient). Thus it may be necessary to ascertain which interpretation the patient has adopted. Credit is also given if the blue square is put under the yellow circle.

Item No. 9: Omission of one circle and/or one square is permitted.

Auditory Choice Vocabulary (*Test No. 7*)

Narrow choice

Example:
Does Little mean *small* or less.

Example:
Does Halt mean slow or *stop.*

Possess:	get	*own*
Timid:	*afraid*	quiet
Ledge:	*shelf*	corner
Precise:	correct	*exact*
Monarch:	president	*king*
Twine:	*string*	cotton
Notion:	*idea*	plan
Vacant:	*empty*	open
Compel:	order	*force*
Nourish:	*feed*	provide
Omen:	risk	*warning*
Tedious:	*boring*	difficult
Elevate:	move	*raise*
Onus:	task	*burden*
Drastic:	*extreme*	dangerous
Ramble:	stray	*wander*
Hazard:	fright	*danger*
Strive:	*try*	work
Wily:	*cunning*	clever
Segment:	*piece*	sample
Intrepid:	strong	*brave*
Nullify:	finish	*cancel*
Anecdote:	*story*	record
Disperse:	arrange	*scatter*
Replica:	*copy*	model
Subside:	disappear	*sink*
Turbid:	*muddy*	sticky
Oblique:	*slanted*	twisted
Peruse:	consider	*read*
Prudent:	accurate	*careful*

Score (ex 30)__________

Wide choice

Example:
Does Shut mean speak or *close.*

Example:
Does Heap mean *pile* or float.

Rely:	*depend*	dry
Trench:	*ditch*	shoot
Scarce:	lovely	*rare*
Mingle:	*mix*	circle
Banner:	happy	*flag*
Pilfer:	*steal*	leap
Remote:	*distant*	cheat
Outcome:	fly	*result*
Amend:	light	*change*
Fibre:	*thread*	flood
Lethal:	arrive	*deadly*
Uphold:	*support*	age
Rile:	wheel	*annoy*
Vigour:	*energy*	remove
Serene:	rope	*calm*
Insolent:	*cheeky*	foreign
Ballad:	*song*	animal
Robust:	beg	*strong*
Inhale:	*breathe*	teach
Adept:	*skilful*	cloud
Kiln:	*oven*	paint
Cavalcade:	name	*procession*
Lure:	icy	*tempt*
Sever:	crown	*cut*
Vapour:	disgraceful	*gas*
Bland:	*mild*	crush
Malice:	tie	*spite*
Dilate:	instant	*expand*
Potent:	*powerful*	shiver
Lucid:	relax	*clear*

Score (ex 30)__________

Object Naming and Object Naming Recognition (*Test No. 8*)

Objects (*and acceptable alternative names*)

1. Bottle opener (opener, also can opener, tin opener if the dual purpose 'coke' can opener is used).
   Recognition: Corkscrew Wrench Bottle opener
2. Key
   Recognition: Key Bolt Chain
3. Glove
   Recognition: Glove Sleeve Bracelet
4. Onion
   Recognition: Carrot Onion Potato
5. Ring
   Recognition: Necklace Brooch Ring
6. Candle
   Recognition: Lamp Candle Torch
7. Rubber (eraser)
   Recognition: Rubber Elastic band Sponge
8. Compasses (compass—both singular and plural names are in common use).
   Recognition: Ruler Set square Compasses
9. Plug
   Recognition: Switch Plug Fuse
10. Thimble
    Recognition: Needle Thimble Cotton reel
11. Button
    Recognition: Button Zip Shoelace
12. Scissors
    Recognition: Knife Razor Scissors
13. Clothes peg (peg)
    Recognition: Safety pin Paper clip Clothes peg
14. Nail
    Recognition. Nail Screw Drawing pin
15. Pencil sharpener (sharpener)
    Recognition: Potato peeler Pencil sharpener Cheese grater

Description Naming and Description Naming Recognition (*Test No. 9*)

1. What do we call the frame which is covered in cloth or paper and flown by children on windy days?—Kite
   Recognition: Balloon Kite Boomerang
2. What is the name of the flat shiny cutting part of a knife or sword?—Blade
   Recognition: Blade Saw Chopper
3. What do we call the instrument that is used by dentists or roadworkers to make holes?—Drill
   Recognition: Drill Shovel Needle
4. What is the name of the bird that flies at night and hoots?—Owl
   Recognition: Pigeon Owl Bat
5. What is the name of the short wooden club carried by policemen?—Truncheon or baton
   Recognition: Flag Whip Truncheon
6. What is the name of the long thin neck on a kettle or watering can, through which the water is poured?—Spout
   Recognition: Spout Pipe Gutter
7. What is the name of the jar or ornament in which we keep flowers?—Vase
   Recognition: Jug Tin Vase
8. What do we call the end of a shirt or blouse sleeve where the buttons are found?—Cuff
   Recognition: Cuff Belt Collar
9. What do we call the large grey animal with a trunk?—Elephant
   Recognition: Rhino Elephant Wolf
10. What is the name of the instrument used for plucking out hairs or picking up small objects?—Tweezers
    Recognition: Pliers Tweezers Scissors
11. What is the name of the net or canvas bed that we hang up in order to lie on it?—Hammock
    Recognition: Couch Bunk Hammock
12. What is the name of the instrument that men use to shave their faces?—Razor. (If reply is 'shaver' ask what the other name for it is)
    Recognition: Chisel File Razor
13. What do we call the small winged insect that makes honey and stings?—Bee
    Recognition: Butterfly Spider Bee
14. What is the name of the thin grey dust that remains after something has burned, like a cigarette?—Ash
    Recognition: Ash Cinders Charcoal
15. What do broadcasters speak into so that they might easily be heard?—Microphone or mike
    Recognition: Typewriter Microphone Gramophone

Brain (1978), **101**, 187–191

NOTICES OF RECENT PUBLICATIONS

Nonstriatal Dopaminergic Neurons. (Advances in Biochemical Psychopharmacology, Volume 16). Edited by E. COSTA and G. L. GESSA. 1977. Pp. 728. New York: Raven Press. Price $57.00.

This book consists of about 100 articles contributed by 200 authors. Interest in non-striatal dopaminergic neurons is strongly encouraged by the theory that schizophrenia is caused by overactive dopaminergic neurons. These can obviously not be the well-known nigrostriatal neurons, and this fact has intensified the search for dopaminergic neurons elsewhere. One group of neurons, termed mesocortical, was found in the deeper layers of certain regions of the cerebral cortex, and the first part of the book describes their distribution and some pharmacological and physiological properties. Another group, which has been known for a longer time, is formed by the mesolimbic dopaminergic neurons, exemplified by the nucleus accumbens, and scattered chapters of the book deal with differences in the responses of these and the nigrostriatal neurons. An interesting finding is that those antipsychotic drugs which cause few extrapyramidal side effects are causing greater changes in dopamine metabolism in mesolimbic than in nigrostriatal neurons. A large part of the book deals with topics not related to ætiology or treatment of psychoses: dopaminergic neurons in the median eminence and arcuate nucleus with all their endocrinological implications, dopamine-containing SIF cells (small, intensely fluorescent cells in sympathetic ganglia), and dopamine neurons in the renal vascular bed and the carotid body. Other chapters bring pharmacological characteristics as well as autoregulatory properties of dopaminergic systems and their interaction with cholinergic and GABA containing neurons. The final chapters return to the original quest by reporting clinical observations trying to assess the relation between dopaminergic neurons and mental disease.

The book will not only be of interest to readers interested in the psychiatric aspect of the role of dopamine, but to specialists in many other fields in which cells containing dopamine play an integral part. It is well produced and each contribution is accompanied by a list of references.

M. VOGT

Substance P. Nobel Symposium 37. Edited by ULF S. VON EULER and BENGT PERNOW. 1977. Pp. 360. New York: Raven Press. Price $30.00.

Substance P, a vasodilator polypeptide first extracted from intestine and brain, and for forty years elusive to satisfactory analysis because purification of extracts containing it led to instability of the active principle(s), has now become one of the most popular subjects of research by neurochemists. Isolated in pure form by Chang and Leeman who were really looking for other hypothalamic polypeptides, it was identified as an undecapeptide, its structure determined and confirmed by synthesis. The history of this discovery (Chapter 2 of the book) makes fascinating reading, and so does the description of its distribution in the brain and gastro-intestinal tract, as illustrated in a paper by Hökfelt and six Swedish colleagues and by another article by Mroz, Brownstein and Leeman. The occurrence of substance P in 20 per cent of primary sensory neurons, its release on stimulation of dorsal roots, the observation that its injection into cerebral ventricles produces analgesia, and its very prolonged membrane action on cells of the dorsal horn which react to noxious heat, suggest a role in nociceptive pathways, particularly those characterized by slow, progressive build-up of excitation. Certain cell groups and terminals in well localized parts of the brain contain substance P, and it is obvious that the discovery of its role within the central and peripheral nervous system is a challenging problem. For anybody interested in this new development, the book represents an excellent source of the information as far as it was available at the symposium which took place in June 1976.

M. VOGT

Nutrition and the Brain. Volumes 1 and 2. Edited by R. J. WURTMAN and J. J. WURTMAN. 1977. New York: Raven Press. Price $30.00 each. Vol. 1. Determinants of the Availability of Nutrients to the Brain. Pp. 336, Vol. 2. Control of Feeding Behaviour and Biology of the Brain in Protein-Calorie Malnutrition. Pp. 523.

In these two volumes different authors have written about various processes that influence the nutrition of the brain. This remit has been interpreted perhaps too broadly; for example, in the first chapter of Volume 1 there is a lengthy review of the diet of primates. This unusual comparative account of diets is included because 'nutrition-brain interactions form a complex homeostatic regulatory system evolved through natural selection'. The rest of the first volume includes chapters of closer relevance to brain-nutrition—energy metabolism, regulation of amino acids, availability of the B vitamins and choline. The second volume starts with a chapter on the control of eating behaviour. This extensive review (827 references) includes a section on the role of the hypothalamus and the participation of neurotransmitters. The developing brain is particularly susceptible to undernutrition and malnutrition. The effects of protein or protein-calorie malnutrition on the brain and behaviour are also covered.

Unfortunately although these are well-written chapters, at least some of the subject has already been covered in recently published books.

A. N. DAVISON

Drive and Reinforcements: Behavioural Studies of Hypothalamic Function. By JAMES OLDS. 1977. Pp. 140. New York: Raven Press. Price $10.50.

James Olds, while working with Peter Milner in Hebb's laboratory at McGill University in 1953, made the discovery that electrical stimulation of some regions of the brain is rewarding, when he observed that rats would return repeatedly to a place where the stimulation was given. He proved that the stimulation was rewarding by showing that animals would work to obtain the stimulation, by, for example, pressing a lever, running through a maze, or crossing a shock grid. Olds then mapped the brain to determine which areas if stimulated would support self-stimulation, and found that many self-stimulation sites were grouped along the course of the medial forebrain bundle. He next investigated the nature of the reward produced, and found for example that at some brain sites hunger increased the self-stimulation rate. Working with colleagues, he went on to investigate the pharmacology of reward by determining whether rats would learn to self-inject their brains with small quantities of neurotransmitters, and although learning could not be demonstrated, it was an interesting and potentially useful approach to the problem. Next he and his colleagues investigated neuronal activity during brain-stimulation reward and natural reward, and found some evidence in the rat that neurons in the hypothalamus had activity related to these processes. The neurophysiological analysis was then extended to the investigation of the effects of reinforcement by recording neuronal activity during learning, and changes occurring in different brain regions during learning were described and analysed. In this book, written not long before his death in 1976, Olds offered us a first-hand account of his own very original series of investigations and discoveries, and a review of others, into the neural substrates of reward and reinforcement, and provided us with some of his thoughts on the operation of these processes. The book includes chapters on intracranial electrical self-stimulation, on the effects of brain lesions on self-stimulation, on the role of catecholamines in reward, and on single unit studies of drive and reinforcement.

E T. ROLLS

Tissue Hypoxia and Ischemia. Edited by M. REIVICH, R. COBURN, S. LAHIRI and B. CHANCE. Advances in Experimental Medicine and Biology, Vol. 78. 1977. Pp. 385. New York: Plenum Press. Price $45.00.

This multi-author book is based on the proceedings of a symposium held in the University of Pennsylvania, USA. It is subdivided into four sections, one on the biochemistry of physiological oxygen sensors, two on the mechanism of oxygen sensing in tissues and the last on the circulatory and metabolic aspects of cerebral hypoxia and ischæmia.

In the first section conceptual problems concerning what constitutes a molecular oxygen sensor and the transduction process are considered. Evidence is presented that cytochrome a, a^3 is a prime candidate for the sensitive matching of oxygen supply to oxygen demand in normoxia. Other candidates include P-450 (the microsomal enzyme which is found in large quantities in the liver), monoxygenases, myoglobin and hæmoglobin. A number of steps must take place between the molecular sensing of oxygen, and the reaction of the effector system and the possibility of H^+ ion amongst others as the mediator is thought attractive, since it would provide a common mechanism for both normoxic and hypoxic states. The concept of the physiological occurrence of hydrogen peroxide in mammalian tissues has received experimental support in recent years and so consideration is given to the possible role played by the peroxisomal enzymes (catalase, urate, L-αhydroxyacid and D-aminoacid oxidases) in the biochemical pathways for oxygen sensing mechanisms. The possibility that oxygen intermediators and hydroperoxides may constitute part of a chemical system able to sense oxygen tension in the tissue is also discussed.

Possible explanations for the mechanisms of oxygen sensing in tissues that include transcellular or transmembranous current formation are outlined in the second and third sections. Various hypotheses explaining pO_2-dependent mechanical tension in vascular smooth muscle are discussed including the idea that it may be mediated by a mechanism other than by the inhibition of ærobic energy production. The mechanism of oxygen-induced contraction of the ductus arteriosus is discussed and it is suggested that E-type prostaglandins may be involved in the maintenance of patency of the fœtal ductus and that, as the pO_2 rises at birth, the relaxant effect of prostaglandins will decrease, thereby facilitating the oxygen-triggered contraction that results in its closure. It is generally accepted that acute hypoxia induces vasoconstriction of the small muscular pulmonary arteries. Evidence for and against the role of mediators rather than a smooth muscle cell oxygen receptor in the pulmonary vasculature is presented. It is concluded that there is little evidence for an oxygen sensor in the coronary vasculature and that the mediator of vasodilatation appears to arise in the parenchymal tissue rather than in vascular smooth muscle. Evidence is presented in favour of adenosine as mediator for the regulation of blood flow in cardiac and skeletal muscle. The oxygen-linked response of carotid chemoreceptors and the effect of a variety of influences on it are described. However, the mechanisms of chemosensitivity are not clear but may involve the release of a 'transmitter substance', the conditioning of certain nerve endings or the contraction of Type II cells. Evidence is presented that the glomus cells of the carotid body contain catecholamines—predominately dopamine—and it is suggested that endogenous catecholamines may act to modulate chemoreception through activation of an adenylate cyclase-cAMP system.

The characteristic features of hypoxic hypoxia, both at normal and reduced perfusion pressures, as well as of complete and incomplete ischæmia and how the metabolic changes relate to irreversible neuronal damage, are discussed in the last section. Studies in which changes in metabolites and NADH fluorescence indicate the heterogeneity of response to cerebral oligæmia are presented, and it is suggested that inhomogeneous flow reduction is the most probable cause, or homogeneous flow reduction coupled with a heterogeneous metabolic rate would have the same result. Changes in cyclic nucleotide, in pO_2 and ion fluxes in various experimental models of cerebral hypoxia are described. Abnormalities in the control mechanisms regulating cerebral blood flow as well as disorders of cerebral metabolism are described in patients with stroke and in various animal preparations. The effects of hypovolæmic shock on cerebral blood flow and its regulation as well as on brain metabolism and mitochondrial function are described.

The 32 chapters are reasonably authoritative and well written and include many informative illustrations, figures and tables. A comprehensive list of references is also appended to each. The volume was photographed from the typescript submitted by the authors, a method that allows rapid publication. This should also ensure a reasonable price so that at a cost of $45 the book seems to be rather expensive. The subjects encompassed by this symposium are varied, ranging from molecular biochemistry to clinical research in cerebrovascular disease. It is therefore difficult to know to whom this volume is principally directed, though the hope was to promote an interdisciplinary discussion of oxygen sensors in various tissues and to examine the effects of hypoxia on different organs, including the brain. This book will be of some interest to anyone with a working knowledge of tissue hypoxia and ischæmia, but whether it will achieve its stated objective seems problematical.

D. I. GRAHAM

Chemical Pharmacology of the Synapse. By D. J. TRIGGLE and C. R. TRIGGLE. 1977. Pp. 654. London and New York: Academic Press. Price £20.

This is a book full of valuable information on more than just the pharmacology of the synapse. Although many interactions between ligands and receptors take place at synapses, others occur at sites which are free of nerves, and these are included in the chapter on structure-activity relationship.

Interest and work on transmitters and the molecular aspects of their production, mode of action and metabolism have grown unbelievably fast in the last decade. The book achieves a readable survey of the progress in spite of having to cope with a vast literature, many contradictory statements and a choice of alternative hypotheses. A very important concept which runs through the book is that of the conformational flexibility of the interacting molecules, both of the transmitters and of the receptors, which helps to explain the variability and self-regulating character of many biological responses.

The book will be a fount of information for the pharmacologist, the neurochemist and the general biologist. Each chapter has an extensive list of references, brought up to date by an additional list of publications covering the years 1975 and 1976. Generous use is made of diagrams and Tables reproduced from the literature Sometimes this means that the legend does not explain the abbreviations and symbols used so that the text has to be consulted.

M. VOGT

Peptides in Neurobiology. Edited by HAROLD GAINER. 1977. Pp. 464. New York & London: Plenum Press. Price $41.00.

Peptides occur in low concentration in the central nervous system where they exhibit high potency and specificity. They have both transmitter and hormone-like properties with quite remarkable biological activity.

Thus, the hypothalamic-pituitary complex contains a great variety of oligopeptides which carry specific information generating behaviour patterns in response to environmental needs. There are, for example, remarkable effects of trace amounts of ACTH fragments and vasopressin on memory. There is also no doubt that interest in the neuropeptides was intensified following the discovery of the endogenous peptides. However, although these aspects are covered in *Peptides in Neurobiology* the primary objective of the editor is to provide a scientific groundwork on which an understanding of future advances must rely. The temptation to write on the more speculative features of centrally acting peptides has been resisted.

Detailed consideration of neuroendocrine functions of the releasing factors and of peptides such as nerve growth factor are omitted because they are already well reviewed in the literature. The first section of the book is on biochemical methodology and accounts of fluorescent techniques, radio-immunoassay and immunochemistry. The second part deals with anatomical localization, isolation and identification of CNS peptides (e.g. substance P, neurotensin, TRH, LH-RH, etc.). In the final parts of the book metabolism, pharmacological and behavioural effects of peptides are covered. There is a section on peptides and the invertebrate nervous system. This will be a useful book for the neuroscientist and can be recommended.

A. N. DAVISON

Pathology of Peripheral Nerves. By R. O. WELLER and J. CERVÓS-NAVARRO. 1977. Pp. 225. London: Butterworths. Price £13.50.

There are few books available to pathologists, to clinicians interested in peripheral nerves, or to experimentalists, which deal comprehensively with the technically difficult area between the central nervous system and the effector and sensory organs. This volume attempts to bridge the gap by considering the nerve bundles and axons with brief, apposite references to their peripheral attachments and origins. In reviewing the relevant history (perhaps too briefly), technical methods (far too briefly) and the functional anatomy of normal peripheral nerves, the authors set the scene for the most important part of the book dealing with general pathology of peripheral nerves and the pathology of peripheral nerve diseases. The authors highlight the dangers of producing artefacts which can only be avoided by great care and experience. The sixty-odd pages (just under one third of the book) devoted to tumours of the peripheral nervous system seems disproportionately large considering that there are detailed works on such tumours in most libraries.

The section on techniques will probably be disappointingly superficial to some who do not have the back-up of a versatile histology service but, even so, it might have suited some potential readers to know how the authors' laboratories handle individual, difficult or critical techniques such as formalin-induced fluorescence, individual histochemical methods or silver-impregnation techniques rather than to be referred to other books and papers. The rationale for the use of many of the techniques mentioned is not given.

In the sections dealing with pathology, the authors refer to a great many review articles in describing diseases and syndromes simply without being exhaustive and refer to relevant experimental work. This section, which is the most valuable in the book, is quite up-to-date.

At 6·3 pence per page (or roughly three times that per page for the most valuable section) this book is unlikely to be bought privately.

D. DOYLE

৮,৫৫.
২৬.৯.৮

ISSN 0006-8950

Brain

A Journal of Neurology

Volume 101 Part II June 1978

Variations in Regional Cortical Blood Flow in the Right and Left Hemispheres during Automatic Speech. Bo Larsen, Erik Skinhøj and Niels A. Lassen 193

The Natural History of Intermittent Claudication of the Cauda Equina. J. N. Blau and Valentine Logue 211

A Critical Appraisal of Posterior Fossa Surgery for Communicating Syringomyelia. Bernard Williams 223

The Corticopontine Projection in the Rhesus Monkey. P. Brodal 251

Late Blink Reflex Changes in Lateral Medullary Lesions. B. W. Ongerboer de Visser and H. G. J. M. Kuypers 285

The Sensation of Heaviness after Surgical Disconnection of the Cerebral Hemispheres in Man. S. C. Gandevia 295

Somatosensory Epilepsy. F. Mauguiere and J. Courjon 307

Subacute Spongiform Encephalopathy (Creutzfeldt-Jakob Disease). C. L. Masters and E. P. Richardson Jr. 333

Acetylcholine Receptors and End-Plate Electrophysiology in Myasthenia Gravis. Y. Ito, R. Miledi, A. Vincent and J. Newsom-Davis 345

Notices of Recent Publications 369

OXFORD: AT THE CLARENDON PRESS

Edited by C. G. PHILLIPS
Deputy Editor R. A. HENSON
with the help of

J. HUME ADAMS	R. W. GILLIATT	M. VOGT
A. N. DAVISON	E. C. HUTCHINSON	L. WEISKRANTZ

Assistant Editor E. MACDOUGALL
Secretary and Treasurer J. M. NEWSOM DAVIS

All editorial correspondence, typescripts and books for review to be addressed to The Editor of *Brain*, Hertford College, Oxford, OX1 3BW.

Directions to Authors upon the Preparation of Papers

PAPERS must be typewritten on one side of the paper only and double-spaced, and submitted in duplicate with two sets of figures. In addition to the full title of the paper, authors should supply a 'running title' which will appear at the heads of the pages. *Brain* does not publish preliminary reports of work in progress only exceptionally does it publish detailed studies of a single case. The typescript should be carefully and finally revised before submission to the Editor, so that if the paper is accepted it is ready for the printer. Clarity of style and brevity of expression are essential. Before submitting a paper it is always valuable to obtain the comments of colleagues who are unfamiliar with the work. We refer intending authors to the *Journal of Physiology*'s 'Suggestions to Authors' price 10p post-free from Cambridge University Press, Box 92, 200 Euston Road, London, NW1.

The paper should be accompanied by a declaration in the following terms: 'The work reported in the attached paper entitled . . has not been, and is not intended to be, published anywhere except in *Brain*.'

BIBLIOGRAPHIC REFERENCES should be limited to essential literature; they should be listed at the end of the paper in alphabetical order, and not numbered *In the case of a Journal*: author's name, date of publication in brackets. are followed by the title of the paper, the name of the Journal *in full* and underlined for italics, the volume number and the first and last page numbers of the paper quoted, both in Arabic numerals. *In the case of a book*: author's name, date of publication in brackets, title of book underlined for italics, place of publication, publisher's name, chapter and page numbers in Arabic numerals. Works by the same author should be given in chronological order, and if there be more than one in a year, they are marked *a*, *b*, *c*, etc.; when an author's name recurs a short line is used. *In the text* numbered references are not used, but the author's name is followed by the appropriate year in brackets.

ILLUSTRATIONS should, where possible, be line drawings in Indian ink on separate white boards, numbered, and with the author's name on the back Drawings and other illustrations should not exceed twice the size of the reproduction and thus lines must be thick enough to show up after reduction This applies also to the lettering and numbering which the authors are asked to provide Legends should be on separate sheets and numbered. Desired positions of tables and figures should be marked by writing instructions enclosed within lines and brackets, e g. (*Table 3 near here*) or (*Fig. 4 near here*).

Half-tone photographs must be kept to a minimum Excellent photographs with clear contrast are essential, especially for the reproduction of electron micrographs. Authors may be asked to contribute to their cost. There should be a bar on all micrographs giving magnification, e.g. $1\ \mu m$

Authors are asked not to reprint their papers, or to authorize others to do so, without first consulting the Oxford University Press (Academic Division), Walton Street, Oxford, OX2 6DP

Fifty free offprints are sent to the authors, who may order more direct from Oxford University Press, Walton Street, Oxford, OX2 6DP when they get their proofs.

Subscription rate for an annual volume of four issues. £19.00 ($42) post free, or for subscribers resident in the U.K £16.50. Single Issue: £5 00 ($12) net, postage extra.

Please address correspondence on business matters as follows:

Subscriptions to the current volume: Subscriptions Department, Oxford University Press, Press Road, Neasden, London, NW10 0DD.

Orders and inquiries for back numbers: Wm. Dawson & Sons Limited, Cannon House, Folkestone, Kent

Inquiries about advertising, offprints and copyright: Academic Division, Oxford University Press, Walton Street, Oxford, OX2 6DP.

Brain

A Journal of Neurology

Volume 101 Part II June 1978

Variations in Regional Cortical Blood Flow in the Right and Left Hemispheres during Automatic Speech. Bo Larsen, Erik Skinhøj and Niels A. Lassen 193

The Natural History of Intermittent Claudication of the Cauda Equina. J. N. Blau and Valentine Logue 211

A Critical Appraisal of Posterior Fossa Surgery for Communicating Syringomyelia. Bernard Williams 223

The Corticopontine Projection in the Rhesus Monkey. P. Brodal 251

Late Blink Reflex Changes in Lateral Medullary Lesions. B. W. Ongerboer de Visser and H. G. J. M. Kuypers 285

The Sensation of Heaviness after Surgical Disconnection of the Cerebral Hemispheres in Man. S. C. Gandevia 295

Somatosensory Epilepsy. F. Mauguière and J. Courjon 307

Subacute Spongiform Encephalopathy (Creutzfeldt-Jakob Disease). C. L. Masters and E. P. Richardson Jr. 333

Acetylcholine Receptors and End-Plate Electrophysiology in Myasthenia Gravis. Y. Ito, R. Miledi, A. Vincent and J. Newsom-Davis 345

Notices of Recent Publications 369

JOURNAL OF MENTAL DEFICIENCY RESEARCH

Editor: Dr B. W. Richards

THE JOURNAL OF MENTAL DEFICIENCY RESEARCH contains original research on medical and psychological problems relevant to mental subnormality.

Recent articles include:

The Recurrence of Mongolism in Sibships, B. W. Richards

Serum Cholinesterase (Pseudocholinesterase) in Down's Syndrome: 1. Phenotype Frequencies at the E_1 and E_2 Loci, Anne H. Drew and A. T. Rundle

The Use of the Vineland Social Maturity Scale, the Merrill-Palmer Scale of Mental Tests (Non-Verbal Items) and the Reynell Developmental Language Scales with Children in Contact with the Services for Severe Mental Retardation, Judith Gould

Chemical Analysis of an Angiofibroma from a Patient with Tuberous Sclerosis, M. H. Fischer, J. S. Fortune, S. H. Foster and B. H. Gilbert

The Ante-Natal Detection of Down's Syndrome: Some Demographic Aspects, D. P. Forster

Double Autosomal Trisomy: (48,XX,+18,+21): Case Report and Review of Literature, K.-P. Grosse and G. Schwantitz. **Appendix: Results of Dermatoglyphic Analysis,** Danuta Loesch

Interchromosomal Duplication for the Short Arm of Chromosome No. 9: Report of Three Cases Due to a Familial Translocation t(9;11) and One Case with a De Novo 47,XX,+9p Karyotype, C. C. Lin, G. Holman, L Sewell, P. Bowen and B. Bierderman. **Appendix: Results of Dermatoglyphic Analysis,** Danuta Loesch

Published quarterly by
THE NATIONAL SOCIETY FOR MENTALLY HANDICAPPED CHILDREN
Pembridge Hall, 17 Pembridge Square, London W2 4EP

Yearly Subscription £10.00 U.S.A. $30.00

Monographs of the Physiological Society No.34
edited by P.F. Barker, A.D.M. Greenfield, R.A. Gregory, D.K. Hill and P.B.C. Matthews

Corticospinal Neurones

Their Role in Movement
G.C. Phillips and R. Porter
1977, xii + 488pp., £16.80/$ 32.85 **0.12.553950.9**

This book is more than just a compilation of experimental findings. By discussing their personal observations in the context of accumulated knowledge the authors have produced a classic work which will endure long after new research has outdated parts of it. It reviews and analyzes all major work on the corticospinal tract, starting with extensive historical material and terminating with newly published work. The strength of this analysis derives from one or other of the authors having been personally engaged in most of the types of work described. The account of the corticospinal neurones includes their biophysical properties; the distribution of their axons to their targets throughout the neuraxis; their excitatory and inhibitory actions on neurones of the somaesthetic 'relay' nuclei and on those of subcortical and cerebellar motor systems, the sources of their excitatory and inhibitory inputs; and their status as the central cores of the input-output modules of which the 'motor' cortex is composed. The concluding chapter tries to interpret some of the facts of human motor control and perception of movement with reference to the structure and properties of the corticospinal projection in monkeys.

Elements of the Behavioral Code

Francis V. DeFeudis and Patricia A.F. DeFeudis
1977, xii + 390pp., £15.00/$ 29.35 **0.12.208760.7**

Attempts have been made for many years to understand memory in terms of some sort of physical change in the brain. This informative book analyzes and integrates the results of many modern investigations, neurological, neurochemical, neurophysiological, in an attempt to give a rational understanding, in present day terms, of memory and behavioral phenomena. The theory of the "Behavioral Code" presented here is based on findings which have revealed that environment alters neuromorphology. The authors emphasize the biochemical and morphological changes that accompany various informational inputs to the CNS and the associated behavioral modifications. An attempt is made to specify relevant CNS changes which result from the complex interaction of an organism with its environment. A two-factor theory emerges, in which informational inputs to the CNS exert short-term "non-specific" effects on arousal and motivational systems, causing general metabolic changes; and this is followed by long-term enduring structural changes which involve alterations in the amount of synaptic protein synthesized in those particular CNS structures concerned with the processing of specific unputs. This theory is in accord with both "aggregate-field" and "cellular-connectionist" concepts, since it includes events that affect the whole CNS as well as those that persist as memories and which may be specific to synaptic connections of certain functional pathways.

Academic Press
London New York San Francisco
A Subsidiary of Harcourt Brace Jovanovich, Publishers
24-28 Oval Road, London NW1, England
111 Fifth Avenue, New York, NY 10003, USA

An international multidisciplinary journal devoted to all aspects of pain research and management.

PAIN

The Journal of the International Association for the Study of Pain

Editor-in-chief: P.D. Wall, Department of Anatomy, University College London, U.K.

Editorial Board: J.J. Bonica, Seattle, Washington, U.S.A. A. Iggo, Edinburgh, Scotland. J.D. Loeser, Seattle, Washington, U.S.A. W. Noordenbos, Amsterdam, The Netherlands.

Pain provides a forum for original research reports and reviews from the many disciplines involved in the study of this debilitating and seemingly interminable affliction Papers containing current clinical information about the nature, mechanisms and treatment of pain are published in the following areas· anaesthesiology; anatomy; dentistry; general surgery; medicine; neurology; neurosurgery; orthopaedics; pharmacology; physical medicine, physiology; psychiatry; psychology.

Review articles appearing in Volume 3 No. 4 and Volume 4 Nos. 1-4

Sensory decision theory methods in pain research: a reply to Rollman by C.R. Chapman (Seattle, Wash., U.S.A.)

Neurons that subserve the sensory-discriminative aspects of pain by D.D. Price and R. Dubner (Bethesda, Md., U.S.A.)

Serotonin-containing neurons: their possible role in pain and analgesia by R B. Messing and L.D. Lytle (Irvine, Calif. and Cambridge, Mass., U.S.A.)

Pain-signalling systems in the dorsal and ventral spinal cord by S.G. Dennis and R. Melzack (Montreal, Canada)

Phantom body pain in paraplegics: evidence for a central "pattern generating mechanism" for pain by R. Melzack and J.D. Loeser (Montreal, Canada and Seattle, Wash , U.S.A.)

Narcotic analgesics: CNS sites and mechanisms of action as revealed by intracerebral injection techniques by T.L. Yaksh and T.A. Rudy (Madison, Wisc., U.S.A.)

1978 - Volumes 4 & 5 in 8 issues US $ 100.00/ Dfl. 230.00 including postage

Journals are automatically sent by air to the U.S.A. and Canada at no extra cost and to Japan, Australia and New Zealand with a small additional postal charge.

ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS

send your orders and requests for free specimen copies to

in the U.S.A. and Canada:
JOURNAL INFORMATION CENTER
Elsevier's Science Division,
52 Vanderbilt Ave.,
New York, NY 10017

in all other countries:
ELSEVIER/NORTH-HOLLAND
BIOMEDICAL PRESS
P.O. Box 211, Amsterdam,
The Netherlands.

Brain (1978), **101**, 193-209

VARIATIONS IN REGIONAL CORTICAL BLOOD FLOW IN THE RIGHT AND LEFT HEMISPHERES DURING AUTOMATIC SPEECH

by BO LARSEN, ERIK SKINHØJ *and* NIELS A. LASSEN

(From Department of Clinical Physiology and Department of Neurology, Bispebjerg Hospital, and Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark)

INTRODUCTION

LOCALIZATION of the neurophysiological mechanisms involved in speech is based first of all upon the derangements of speech caused by lesions of certain cerebral structures, and upon the interference with speech induced by electrical stimulation of various cortical areas. This has proved that normal speech can be produced only if certain areas and certain pathways within the dominant hemisphere are intact. However, such observations do not give any information about the total cortical involvement in normal speech. As Hughlings Jackson stated: 'To locate the damage which destroys speech and to locate speech are two different things' (Jackson, 1874). The involvement of the non-dominant hemisphere demonstrated in our study emphasizes Jackson's concept. The fundamentally correct approach to the problem of localization of speech functions is, therefore, to follow the pattern of neuronal activation during speech. So far, this has not been very fruitful. Electrophysiological events such as cortical evoked responses (Morrel and Salamy, 1971), slow negative potentials (McAdam and Whitaker, 1971), and EEG correlations (Galin and Ornstein, 1972) afford only a rough localization and are furthermore influenced by artefacts, especially when recorded from the scalp (Elliot and Grabow, 1973).

Measurement of the blood flow in different brain regions appear to be a more precise method for finding the pattern of neuronal activation. This principle is implicit in the ideas formulated by Roy and Sherrington as early as 1890. They pointed out that a close coupling appears to exist between local blood flow, metabolism and functional activity in the brain (Roy and Sherrington, 1890). This close coupling was more firmly documented in the classic review by C. F. Schmidt in 1950, in which he summarized local blood flow measurements in animals, and total hemispheric blood flow and metabolism measurements in man, during various states of brain activity such as coma, normal conscious state and generalized epileptiform convulsions.

With the development of the ^{133}Xe intracarotid injection method, external recording of the blood flow in multiple small regions of hemispheric cortex in man became possible (Høedt-Rasmussen, Sveinsdottir and Lassen, 1966; Lassen and Høedt-Rasmussen, 1966). By this approach, specific alterations in the regional cerebral blood flow, rCBF, have been demonstrated during different forms of brain activity (Ingvar and Risberg, 1967; Risberg and Ingvar, 1973). By measuring the rCBF during voluntary movement of the hand, Olesen (1971) demonstrated that the blood flow in the contralateral sensorimotor hand area increases between 50 to 100 per cent. No significant increase was recorded in the ipsilateral hand area. Using the same hand movement test and cyclotron produced radioactive oxygen, Raichle, Grubb, Mokhtar, Eichling and Ter-Pogossian (1976) showed that in neurologically normal subjects, not only rCBF, but also the regional cerebral oxidative metabolism, increases in the sensorimotor hand area. Thus, under strictly physiological conditions in man, the coupling between local neuronal activity, cerebral metabolism, and rCBF is now well established.

The present study aims at mapping the pattern of cortical activation, induced by a simple automatic speech test which consisted in counting to twenty or reciting the days of the week. The maps represent the associated regional increases in cerebral blood flow. This has been done previously by Ingvar and Schwartz (1974). Using the ^{133}Xe intracarotid injection method and 16 to 32 detectors, they studied the dominant hemisphere and showed that automatic speech resulted in augmented flow values in the pre-motor, the rolandic, and the anterior and middle sylvian regions. Kohlmeyer (1975) found similar changes in the dominant hemisphere during conversation; in three subjects he found no changes in the non-dominant hemisphere. In our study we used the ^{133}Xe intracarotid injection method and a 254 detector imaging device (Sveinsdottir, Larsen, Rommer and Lassen, 1977). We here report local blood flow alterations in the cortex of both the dominant and non-dominant hemispheres in normal subjects performing the automatic speech test. In other studies from our departments, this technique has proved applicable to localizing the somatic sensorimotor cortex for mouth, hand and foot in the rolandic region during various tactile discrimination tests (Roland and Larsen, 1976) and the cortical activity in patients with focal epilepsy (Hougaard, *et al.*, 1976).

PATIENTS AND METHODS

The study population comprises 18 subjects. They were all right-handed. The mean age was 52 years, range 24–72 years. In 9 subjects the left hemisphere and in the other 9 the right hemisphere was studied.

In all subjects the clinical symptoms and the electroencephalographic findings gave indication for carotid angiography in order to exclude space-occupying processes or vascular malformations. The angiography was done with the Seldinger technique and was normal in all subjects. With the patient's informed consent, the procedure was then continued with the flow study using the indwelling internal carotid catheter. The final diagnoses were epilepsy, migraine, psychogenic headache or hysteria. It should be noted that when we use the word normal to describe our material, this term refers first of all to the absence of focal neurological deficits and to the normal angiogram. It may be added, however, that the normality was, in most cases, further confirmed by the demonstration of a normal pneumoencephalogram, ^{99m}Tc-pertechnetate scan, or CT scan. The patients with epilepsy had suffered a few non-focal attacks and the EEG recordings made during the rCBF study did not show any paroxymal activity.

The subjects received either no premedication or a small dose of diazepam. The examination was carried out in a quiet room with the subjects in a physically and mentally relaxed state. Their eyes were covered and their ears plugged with cotton wool. The first measurement was made without the subject speaking and the result is taken to represent the flow value during rest. After an interval of twenty minutes, the speech test was performed. The speaking started half a minute before the isotope injection and was continued during the first minute. The speed of speaking was one word per second. The subject was requested to count repeatedly to twenty or to recite the days of the week, that is, we have studied a type of simple automatic speech not requiring any mental effort, verbal commands or emotional involvement.

In 7 of the subjects the study included two measurements during rest and two during speech.

Methods and Data-processing

The rCBF was measured by injecting ^{133}Xe into the internal carotid artery and recording the initial one-minute clearance of radioactivity from 254 regions of the labelled hemisphere.

The detector system is a computerized multidetector scintillation camera. Its technical data and performance have recently been described in detail (Sveinsdottir *et al.*, 1977) and will therefore only be mentioned briefly: the 254 crystals (8 mm in diameter) are arranged in an orthogonal matrix with 19 columns and 14 rows on a slightly curved surface. The centre-to-centre distance between the crystals is 10 mm. The camera is collimated by a 4 cm thick lead slab with 254 converging cylindrical holes. This converging collimator, having its focus at a distance of 16 cm, yields a magnifying effect of about 1 5 at the level of the surface of the brain 3 cm in front of the collimator. The spatial resolution of the camera was checked by using two line sources of ^{133}Xe in a water bath. At a distance of 3 cm from the collimator, the line sources could be distinguished separately, as long as they were at least 16 mm apart.

About 10 mCi of ^{133}Xe dissolved in 2 ml of isotonic saline is injected as a bolus into the carotid artery and the washout of ^{133}Xe from the hemisphere is followed. The peak count rate for each detector is approximately 1000 counts per second. After two minutes, a TV monitor displays on a semilogarithmic scale the 254 clearance curves corrected for background and remaining activity. From these curves the slopes, taken from fifteen to sixty seconds after the injection, are calculated on-line using a least-square fit. The rCBF is calculated as $D \times 0{\cdot}87 \times 2{\cdot}30 \times 100$ ml/100g/min (Olesen *et al.*, 1971), D being the numerical value of the slope of the clearance in the decimal logarithmic system and expressed in fraction of decade per minute; 0·87 the partition coefficient of ^{133}Xe for brain cortex; 2·30 the conversion factor from decimal to natural logarithm; and 100 the factor needed to obtain flow per 100 grams.

The flow pattern is displayed on a colour TV monitor as an image of coloured squares imitating the spatial arrangement of the detectors and representing the flow values on a 16-level colour scale. The rCBF data are subsequently read into a general data-processing system. In this system, the rCBF data from different measurements can be compared. Areas of interest consisting of several adjacent detector fields can be defined, and statistical operation can be performed. The values are printed out on a teletype or displayed on the TV monitor in colour code.

Within the first minute after injection of the isotope, a blood sample is taken from the internal carotid artery for determination of $PaCO_2$, and the intra-arterial blood pressure is measured. The $PaCO_2$ at the first rCBF measurement is used as a reference value correcting the subsequent rCBF by 4% per 1 mmHg difference in $PaCO_2$ (Olesen, Paulson and Lassen, 1971).

Localization

During the measurement, the subject was lying with the head in a fixed position relative to the scintillation camera. The position was adjusted so that the line between the lateral orbital angle and the external auditory meatus corresponded to the lowest row of the detectors with the external meatus placed opposite to the middle channel in this row. Small radioactive markers were fixed with adhesive tape to the nasion and inion as well as to the vertex half-way between nasion and inion. Immediately before the rCBF measurement, a picture was taken with the scintillation camera for localization of these markers on the image matrix. On this basis the main sulci and gyri were localized approximately, by making use of the proportional system of Talairach and Azikla (1967).

The validity of this localization procedure was checked by studying twelve human skulls of different sizes and shapes. Radioactive markers were placed externally as in the *in vivo* studies. In addition, other markers were placed on the inside of the skull corresponding to the borders between the main cortical regions on the convexity of the hemisphere. In this way it was found that the external markers, together with the proportional system of Talairach, made it possible to determine the position of the internal landmarks within 5 to 15 mm.

The Normal Resting Pattern of rCBF

Twenty-three subjects were studied on the left side and 26 on the right. They all fulfilled the criteria of normality used for the speech study. The 18 subjects in the speech study were all included in this group of 49 who make up our normal material. The hemispheric mean flow averaged 52 ml/100 g/min, but with a range from 36 to 84. In order to compare the rCBF patterns, the rCBF value for each subject were expressed as percentages of the individual hemispheric mean value. By adding all the patterns, *the average rCBF pattern* was obtained for both the left and the right hemisphere (fig. 1).

In order to determine whether such inter-individual differences blur the average picture to any essential degree, we defined 7 large brain areas in all 49 subjects using the method of Talairach and Azikla (1967). The rCBF values in percentage of the individual hemispheric mean were averaged for each of the 7 areas, the number of detectors included per area varying from subject to subject. The grand average for each area was subsequently obtained for the total material (Table 1). Dividing the simple average picture into the same 7 areas gave practically the same result (*see also* Table 1). Thus, despite the individual differences in size and shape of the head, the simple procedure of superimposing the matrices, used in fig. 1, gave an essentially correct normal rCBF distribution pattern.

The normal rCBF pattern is characterized by high flow values in the frontal regions especially in the upper part, where it is on average 12 per cent above the hemispheric mean. A frontal lobe average rCBF value below the hemispheric mean was found in only one of the 49 subjects, having a frontal rCBF 3 per cent below the hemispheric mean. In this patient a pre-senile organic dementia had been suspected, but not definitely established clinically.

TABLE 1. FLOW DISTRIBUTION DURING REST IN 7 AREAS OF 23 LEFT AND 26 RIGHT HEMISPHERES

	Upper frontal %	*Middle frontal* %	*Lower frontal* %	*Upper central* %	*Lower central* %	*Parietal* %	*Temporal* %
Left (n = 23). Mean and SD Areas defined individually for each subject	112±6	106±4	106±5	101±5	99±7	99±7	92±5
Left (n = 23). Mean. Areas defined after adding all 23 hemispheres (*see* fig. 1)	110	106	106	103	102	99	94
Right (n = 26). Mean and SD Areas defined individually for each subject	112±4	107±4	108±4	101±6	99±6	98±5	93±5
Right (n = 26). Mean. Areas defined after adding all 26 hemispheres (*see* fig 1)	113	109	110	103	102	98	94

Values close to the hemispheric mean are found in the parietal region. The temporal regions show the lowest values, on an average 7 per cent below the mean. There is often a band of rather high flow values, 10 per cent above the mean, corresponding to the anterior part of the lateral sulcus, and a 2-3 cm wide band of low values in the central part of the convexity corresponding to the course of the pre- and post-central gyrus. A very similar rCBF pattern was described for normal man by Wilkinson, Bull, du Boulay, Marshall, Russell and Symon (1969) and by Sveinsdottir, Torlöf, Risberg, Ingvar and Lassen (1971-72) using a smaller number of detectors. It should be noted that the normal resting rCBF pattern shows no significant differences between left and right hemispheres.

Reproducibility of rCBF

Repeated resting rCBF measurements were performed within the same study in 24 of the 49 normal subjects. After correcting for possible changes in $PaCO_2$, the results showed a systematic decrease in *mean hemispheric flow* from first to second resting measurement. The decrease averaged 1·5 ml/100 g/min for the left side ($n = 13$) and 5·6 ml/100 g/min for the right side ($n = 11$). Adding these systematic differences to the second resting measurements, the random experimental error was calculated as the standard deviation, $SD = \sqrt{\frac{\Sigma d^2}{2n}}$. For the left hemisphere SD was 3·2 ml/100 g/min, for the right 4 8 ml/100 g/min. Expressed as coefficient of variation, the random error was 6·5 per cent for the left hemisphere (average flow 49 ml/100 g/min) and 8·7 per cent for the right hemisphere (average flow 55 ml/100 g/min).

In order to evaluate changes in *the pattern of rCBF*, we calculated the percentage variations from the individual mean hemispheric flow for both the first and the second resting rCBF measurements. Using the same equation, the random error of the individual regional (one detector) measurement was 8·7 per cent (SD 2·4 per cent). *For the 7 large areas*, defined according to Talairach and each containing at least 14 individual detector fields, the mean difference and the probability for a significant difference between the first and the second resting study were calculated for each area in each subject using the method of paired comparisons. By analysing the differences for the 7 areas in the left as well as in the right hemispheres, no systematic differences were found. For the 7 large areas, the random error of measurement averaged 3·3 per cent (SD 0·6 per cent). However, the individual subject might present significant differences between some of the areas, when the two resting values were compared: thus, in 6 subjects one area, in 6 two areas, in 2 three areas, and in 2 subjects four areas differed significantly. This probably reflects changes in local neuronal activity of brain cortex at the two measurements during rest.

Fig. 2 demonstrates the reproducibility of the rCBF pattern during rest in the 13 left hemispheres and the 11 right hemispheres. The pictures are based on comparing the two resting studies each normalized to its hemispheric mean value using the equation $\Sigma_i (R_2/\bar{R}_2)/(R_1/\bar{R}_1) \times 100$, where R_1 and R_2 are the rCBF values from the first and the second resting study, respectively, and $\bar{R}_1$ and $\bar{R}_2$ the corresponding mean hemispheric flows. As seen from fig. 2, the average rCBF pattern is practically unchanged from the first to the second resting study.

RESULTS

As compared to the resting state no systematic changes were observed in $PaCO_2$, mean arterial blood pressure or pulse rate during the speech test.

1. *The Mean Hemispheric Blood Flow*

In the 9 subjects in which mean flow was measured in the *left* hemisphere, there was no significant change from rest to speech: an average increase of 3 per cent was seen, range 16 to 17 per cent, $P > 0{\cdot}1$ (Wilcoxon test for paired differences).

TABLE 2. DIFFERENCES IN THE FLOW PATTERN DURING REST AND DURING AUTOMATIC SPEECH IN 10 AREAS IN 9 LEFT HEMISPHERES

No.	Mean hemispheric CBF ml/100 g/min			*rCBF difference Talk—Rest, both in per cent of mean hemispheric CBF*									
	Control rest	*Test talk*		*Upper frontal*	*Post upper frontal (pre-motor)*	*Middle frontal*	*Lower frontal*	*Upper central*	*Lower central*	*Middle lower central*	*Parietal*	*Temporal*	*Post. sup. temporal*
1	44	44	n	27	8	34	21	15	15	8	45	45	17
			$\bar{D}$	+2·2	+11·8	−5·1	−2·3	−3·4	+12·1	+21·9	−6·6	+6·5	+12·7
			SED	±3·1	±3·0	±1·4	±1·2	±3·1	±3·9	±4·1	±2·0	±2·1	±3·0
			P	n.s	<0·01	<0·001	n.s.	n.s.	<0·01	<0·005	<0·005	<0·005	<0·001
2	44	45	n	30	13	37	32	18	14	9	48	39	14
			$\bar{D}$	+22·0	+29·8	−0·1	−3·5	+12·2	+17·3	+23·9	−9·4	−0·9	+11·2
			SED	3·0	±4·2	±1·9	±1·8	±1·9	±3·8	±4·5	±1·5	±1·6	±2·2
			P	<0·001	<0·001	n.s.	n.s.	<0·001	<0·001	<0·001	<0·001	n.s.	<0·001
3	36	41	n	26	11	34	32	20	12	8	60	41	11
			$\bar{D}$	+10·8	+18·5	+3·1	−1·0	+3·0	+12·4	+16·9	−8·2	+5·4	+8·5
			SED	±2·1	±2·3	±1·9	±2·0	±2·0	±3·4	±3·5	±1·0	±1·3	±2·1
			P	<0·001	<0·001	n.s.	n.s.	n.s.	<0·005	<0·005	<0·001	<0·001	<0·005
4	56	57	n	37	9	27	39	15	12	4	35	41	11
			$\bar{D}$	+3·6	+15·6	−4·7	−2·7	+9·9	+11·0	+14·3	−0·7	+4·8	+6·1
			SED	±1·9	±1·7	±1·6	±1·4	±2·1	±2·0	±3·0	±1·0	±1·0	±1·1
			P	n.s.	<0·001	<0·01	n.s.	<0·001	<0·001	<0·02	n.s.	<0·001	<0·001
5	63	53	n	30	6	31	29	12	12	9	43	45	7
			$\bar{D}$	−4·5	+7·6	−9·0	+1·7	−2·3	+13·3	+20·6	−4·7	+10·4	+18·6
			SED	±2·0	±2·2	±1·8	±2·5	±3·2	±3·6	±3·3	±1·8	±1·8	±3·5
			P	n.s.	<0·02	<0·001	n.s.	n.s.	<0·005	<0·001	<0·02	<0·001	<0·005

			n	23	8	23	27	14	12	3	50	44	22
6	67	63	$\bar{D}$	+1·6	+17·8	−5·7	−0·9	+7·1	+11·1	+21·7	−4·6	+6·5	+13·6
			SED	±3·2	±2·7	±2·0	±1·3	±2·4	±2·7	±4·4	±1·4	±1·6	±1·7
			P	n.s.	<0·001	<0·01	n.s.	<0·01	<0·005	<0·05	<0·005	<0·001	<0·001
			n	25	6	27	37	13	13	9	34	43	10
7	54	63	$\bar{D}$	+0·9	+11·2	−4·3	−5·2	−1·5	+7·6	+12·8	−9·0	+0·2	+18·6
			SED	±2·5	±2·9	±2·0	±2·0	±3·3	±3·5	±3·2	±2·8	±2·3	±2·6
			P	n.s.	<0·02	<0·05	<0·05	n.s.	<0·05	<0·005	<0·005	n.s.	<0·001
			n	26	9	28	37	11	13	4	38	60	11
8	48	49	$\bar{D}$	+11·2	+26·8	−6·6	−2·6	−7·9	+12·9	+22·5	−7·3	+2·1	+9·8
			SED	±4·1	±6·7	±2·5	±2·2	±2·6	±3·2	±6·6	±2·5	±2·2	±2·4
			P	<0·02	<0·005	<0·02	n.s.	<0·02	<0·005	<0·005	<0·01	n.s.	<0·005
			n	32	6	24	28	15	15	8	54	59	14
9	37	43	$\bar{D}$	+0·4	+12·0	−9·0	−5·0	−9·6	+11·6	+16·8	−5·3	+5·2	+10·9
			SED	±2·7	±2·9	±2·0	±2·9	±5·0	±2·7	±2·2	±2·0	±1·7	±2·1
			P	n.s.	<0·01	<0·001	n.s.	n.s.	<0·001	<0·001	<0·01	<0·005	<0·001
P					+	−			+	+	−	+	+
Total: sign test				n.s.	<0·01	<0·05	n.s.	n.s.	<0·01	<0·01	<0·01	<0·05	<0·01

n = number of regions (detectors). $\bar{D}$ = mean difference for paired detectors. SED = standard error of difference. *P* = probability (method of paired comparisons).

TABLE 3. DIFFERENCES IN THE FLOW PATTERN DURING REST AND DURING AUTOMATIC SPEECH IN 10 AREAS IN 9 RIGHT HEMISPHERES

	Mean hemispheric CBF ml/100 g/min			*rCBF difference Talk—Rest, both in per cent of mean hemispheric CBF*									
No.	*Control rest*	*Test talk*		*Upper area*	*Post upper frontal (pre-motor)*	*Middle frontal*	*Lower frontal*	*Upper central*	*Lower central*	*Middle lower central*	*Parietal*	*Temporal*	*Post sup. temporal*
10	73	75	n	34	9	29	27	16	14	4	52	46	11
			$\bar{D}$	+2·3	+7·4	+1·3	+3·0	−11·2	+1·6	+5·5	−4·4	+6·2	+12·9
			SED	±1·6	±4·1	±1·3	±1·7	±1·8	±2·3	±2·0	±1·5	±1·8	±2·3
			P	n.s.	n.s.	n.s.	n.s.	<0·001	n.s.	n.s.	<0·01	<0·005	<0·001
11	42	52	n	27	9	24	28	14	13	4	29	59	19
			$\bar{D}$	−2·7	−5·4	−7·7	−4·4	−0·9	+14·8	+23·8	−3·7	+5·3	+13·6
			SED	±1·6	±1·9	±1·7	±1·5	±2·4	±2·6	±5·5	±1·8	±1·2	±1·9
			P	n.s.	<0·05	<0·001	<0·01	n.s.	<0·001	<0·05	<0·05	<0·001	<0·001
12	46	51	n	32	7	26	27	18	12	3	53	42	10
			$\bar{D}$	+7·1	+16·3	+3·7	+3·5	−1·2	+3·4	+13·0	−3·3	+7·9	+11·4
			SED	±1·6	±1·6	±1·4	±1·2	±1·1	±1·7	±3·5	±1·0	±1·1	±3·0
			P	<0·001	<0·001	<0·02	<0·01	n.s.	n.s.	<0·05	<0·005	<0·001	<0·005
13	61	69	n	37	7	27	35	19	14	14	50	43	9
			$\bar{D}$	+9·9	+28·9	+0·4	−7·6	−1·8	+10·6	+10·6	−7·0	−0·3	+3·1
			SED	±2·5	±4·4	±2·2	±1·3	±2·2	±2·2	±2·2	±1·3	±1·5	±2·4
			P	<0·001	<0·001	n.s.	<0·001	n.s.	<0·001	<0·001	<0·001	n.s.	n.s.
14	46	50	n	32	7	28	32	17	14	5	45	55	11
			$\bar{D}$	+1·7	+19·3	−2·7	−2·7	−8·9	+17·8	+23·2	−2·2	+2·6	+6·2
			SED	±3·6	±5·1	±1·9	±2·3	±2·9	±3·6	±7·3	±2·1	±1·5	±2·3
			P	n.s.	0·01	n.s.	n.s.	0·01	0·001	0·05	n.s.	n.s.	0·05

			n	28	9	27	33	17	15	2	40	45	12
15	84	86	$\overline{D}$	+4·2	+7·8	−1·4	+3·9	−3·7	+0·5	+14·0	−3·0	+3·0	+8·6
			SED	±1·2	±1·4	±2·0	±1·9	±1·6	±2·1	±4·0	±1·4	±1·2	±2·3
			P	<0·005	<0·001	n.s.	<0·05	<0·05	n.s.	n.s.	<0·05	<0·02	<0·005
			n	37	11	26	36	18	14	5	37	53	20
16	63	74	$\overline{D}$	+5·9	+9·4	−2·8	−2·5	−10·9	+15·5	+30·4	−11·3	+1·6	+4·0
			SED	±1·9	±2·1	±1·6	±1·8	±2·7	±4·2	±5·6	±3·5	±1·5	±3·1
			P	<0·005	<0·005	n.s.	n.s.	<0·001	<0·005	<0·01	<0·005	n.s.	n.s.
			n	31	6	23	37	16	18	5	38	50	10
17	70	76	$\overline{D}$	−1·9	−1·5	−3·7	−0·1	+5·3	+5·6	+10·8	−2·2	+0·9	+7·9
			SED	±1·1	±2·1	±1·2	±1·4	±1·4	±1·6	±5·2	±1·1	±1·2	±2·5
			P	n.s.	n.s.	<0·01	n.s.	<0·005	<0·005	n.s.	n.s.	n.s.	<0·02
			n	33	7	23	33	13	13	4	38	53	17
18	38	39	$\overline{D}$	+2·3	+17·0	−12·6	−7·3	−14·0	+10·5	+30·8	−16·6	+3·3	+13·4
			SED	±2·7	±5·3	±4·3	±2·7	±4·4	±3·9	±3·9	±2·9	±2·5	±4·4
			P	n.s.	<0·02	<0·02	<0·02	<0·01	<0·02	<0·005	<0·001	n.s.	<0·01
	P								+	+	−		+
Total: sign test				n.s.	n.s.	n.s.	n.s.	n.s.	<0·05	<0·05	<0·05	n.s.	<0·05

n = number of regions (detectors). $\overline{D}$ = mean difference for paired regions. SED = standard error of difference. *P* = probability.

In the 9 subjects in which mean flow was measured in the *right* hemisphere, the mean flow increased significantly from rest to speech: the average increase was 10 per cent, range 2 to 24 per cent, $P < 0{\cdot}01$ (Wilcoxon test).

2. *The rCBF Pattern*

Speech changed in all subjects the rCBF pattern obtained by expressing the measurements as percentages of the mean hemispheric flow. By comparing the average patterns during rest (fig. 3) and during speech (fig. 4), consistent changes are seen. These changes are, however, best shown by dividing each speech picture by the corresponding resting picture and multiplying by 100. The results for the whole material (fig. 5) contrast with the pattern-less pictures that were obtained by comparing the two resting studies to one another in the same manner (fig. 2).

In the *left* hemispheres (upper part of fig. 5), rCBF was increased in (1) the posterior part of the superior frontal region, *viz.* the upper pre-motor area, (2) the lower part of the central region, *viz.* the face area of the rolandic region, and (3) in the posterior superior part of the temporal region, *viz.* the auditory area comprising the Wernicke speech area. No increase was found in the region immediately in front of the lower part of the rolandic area, *viz.* the Broca area. A decrease was found in the parietal region.

In the *right* hemispheres (lower part of fig. 5), the rCBF increases involved the same three areas as on the left side. However, the pre-motor activation was less marked. It is also seen that in the rolandic face area the involvement was more diffuse and confluent with the increases in the temporal region.

In order to localize the increase in the superior frontal region more precisely, additional rCBF measurements were carried out in one left and one right hemisphere. For these measurements, the head was orientated so that the camera viewed the vertex. As shown in fig. 6 the frontal rCBF increase during speech occurs parasagittally. This location would seem to include that of the supplementary motor area on the mesial side of the hemisphere just in front of the pre-central leg area (Penfield and Welch, 1951).

We also analysed the individual changes in the rCBF pattern during speech by defining 10 areas in each of the hemispheres according to the system of Talairach and making paired comparisons for all detector fields inside each area. The average response in the 10 areas was evaluated by a simple sign test considering only areas where significant changes occurred (*see* Table 2 and Table 3). The analysis confirmed statistically the significance suggested by the obvious changes seen in fig. 5. For the *left* hemispheres rCBF, expressed in per cent of the hemispheric mean value, increased significantly by about 15 per cent in the upper pre-motor area, in the lower central area, and in the upper posterior part of the temporal area. For the *right* hemispheres significant increases of about 15 per cent were likewise found in the lower central area and in the upper posterior part of the temporal area. The upper pre-motor area on the right side showed a mean increase of 11 per cent, an increase which did not reach statistical significance. For both the left and the right hemispheres, the parietal area showed a decrease. Another slight decrease was found in the middle frontal area of the left hemisphere.

3. *The Mean Blood Flow and the rCBF Pattern in Repeated Measurements*

In the 3 left-side and the 4 right-side studies in which the measurements were repeated during rest as well as speech within the same study, the mean hemispheric blood flow was lower at the second measurement in both conditions. The resting values decreased on average 6 per cent (range 0 to −20 per cent) and the values during speech 10 per cent (range +2 to −19 per cent). On the other hand, the rCBF patterns during rest and speech did not differ in repeated measurements.

DISCUSSION

Methodological Considerations

The initial slope index is well established as a quantitative index for the blood flow of the grey matter (Høedt-Rasmussen *et al.*, 1967; Olesen *et al.*, 1971; Kanno and Uemura, 1975). During mental activity, alterations in blood flow occur mainly in the grey matter, and this component of cerebral tissue blood flow, therefore, is of the greatest interest for the mapping of functional changes in the brain (Ingvar and Risberg, 1967; Risberg and Ingvar, 1973). It should, however, be emphasized that we record only the initial slope in the parts of the hemisphere supplied by the internal carotid artery. It should also be emphasized that the cortex of the hemisphere is an extremely folded structure. Hence each detector is recording the weighted sum of local blood flows in several layers of grey matter. The absorption of radiation within the tissues means that flow in the outer layers of cortex is recorded with the highest efficiency. Furthermore, the high spatial resolution yielded by the 254-detector imaging device decreases with depth because of overlapping of neighbouring detector fields. The changes found in the rCBF, therefore, pertain mainly to the superficial part of the lateral cortical mantle of the hemisphere.

The time interval used for calculating the initial slope is from fifteen to sixty seconds after isotope injection. We therefore integrate all the transient changes in blood flow which occur during that period of time. It is conceivable that the cortical areas involved in a specific task, for example, automatic speech, are activated for a fraction of the time interval only. If so, the local metabolism and the blood flow may not be measurably altered. Furthermore, the method obviously does not give any information about the temporal relation between the activation of the different cortical areas.

The fact that our main results are based upon differences in rCBF between the conditions of rest and of automatic speech may, however, imply a more important limitation than that due to grossness of spatial and temporal resolution. We do not know what the brain is doing during ‘rest’. Some of the areas involved in automatic speech may be functioning also during the ideation characterizing the ‘resting’ state. In such areas, then, no change would be detectable.

Changes in Mean Hemispheric Blood Flow

As first pointed out by Ingvar and Risberg (1967), the effect of mental activity upon rCBF can be regarded as consisting of two components: global variations, reflected by changes in the mean hemispheric blood flow, and regional variations, reflected by changes in the rCBF pattern. This mode of interpreting the data is in accordance with the findings of general changes as well as specific local changes in the EEG during mental activity (Homskaya, 1975).

We have shown that a second rCBF measurement during rest normally shows a decrease in the mean hemispheric blood flow. The pattern of rCBF, however, remains unchanged. The decrease in mean flow, which was more pronounced in the right hemisphere than in the left, may reflect changes in the subject's general arousal, activation and vigilance. The mere fact that, during successive rCBF recordings, the subject becomes accustomed to the situation, may thus induce an habituation influencing the general cortical tone—as expressed by the general metabolic level of the cortex (Betz, 1975).

During automatic speech, the mean hemispheric blood flow on the left side did not change significantly, but the 3 per cent decrease that could have been expected from the repeated studies during rest was not found.

In the speech measurements performed on the right side, however, the mean hemispheric blood flow was significantly higher than during the preceding rest, on the average 10 per cent higher. Recalling that on the right side a systematic decrease of 10 per cent could have been expected from the repeated rest studies, the increased flow in the right hemisphere is even more striking.

As we cannot measure rCBF simultaneously in both hemispheres, the rather surprising difference in the general activation of the right and the left hemispheres during automatic speech might be due to random variations in the population studied. The results of intracarotid injection of sodium amytal during automatic speech give strong arguments against a specific role of the non-dominant hemisphere in performing this task (Wada and Rasmussen, 1960). So, if we may assume that our global changes are not caused by random inter-individual differences, we may take them to suggest a more massive involvement of the right than of the left hemisphere in the increased vigilance response during the test.

Changes in the rCBF Pattern

In both hemispheres, the cortical areas specifically activated during automatic speech were two areas involved in the motor performance of speech and one area involved in the auditory perception of speech. The only differences between the two sides consisted in the left hemisphere showing a slightly more marked involvement of the pre-motor cortex and a more distinct pattern of activation in the central and temporal regions, as illustrated in fig. 5. The more distinct pattern of the left side might, however, be due to the lesser global rCBF increase on this side, that is, the diffuse (global) activation could have masked the activation of specific areas to a smaller extent on the left side than on the right.

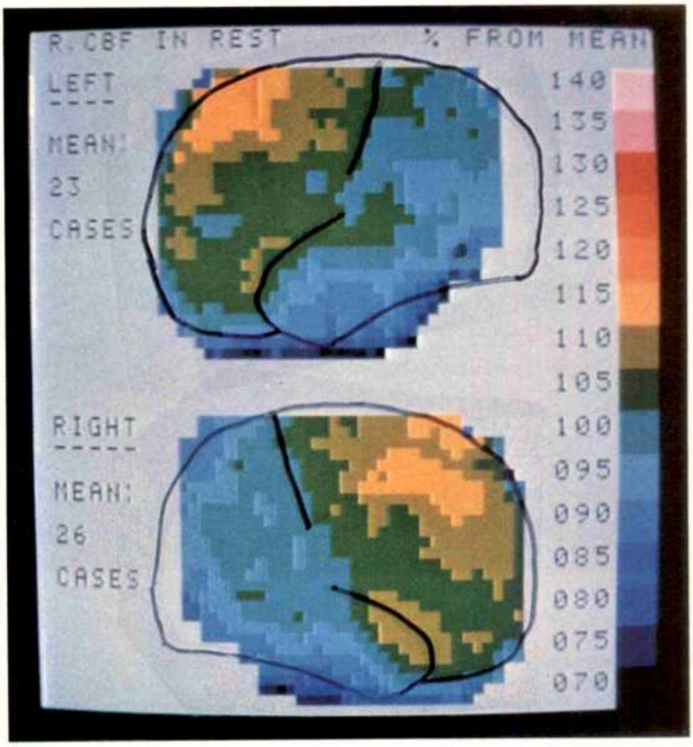


FIG. 1. Normal hemispheric flow distribution during rest. Average from 23 subjects measured in the left hemisphere (*upper*) and 26 subjects measured in the right hemisphere (*lower*).

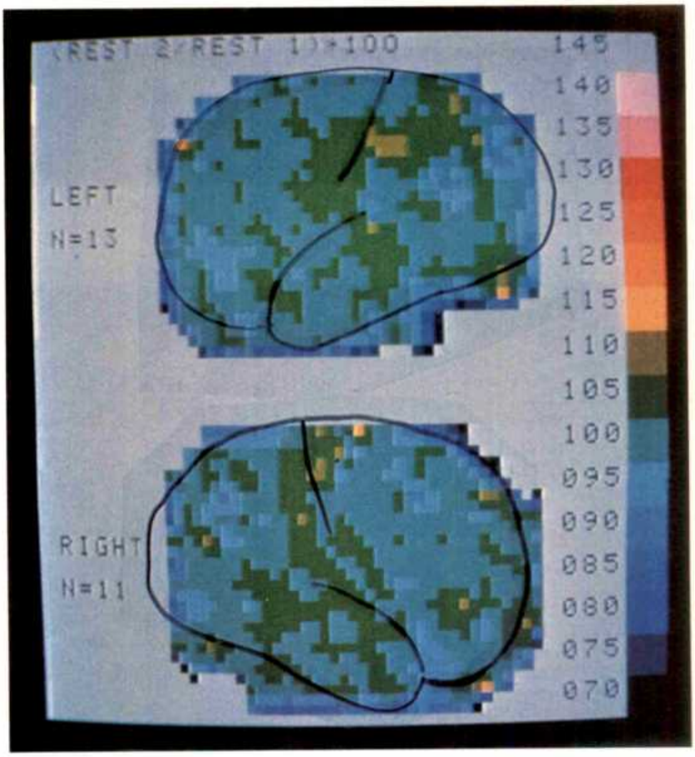


FIG. 2. Average changes in the hemispheric flow distribution from the first to the second resting study. Thirteen left hemispheres (*upper*) and 11 right hemispheres (*lower*).

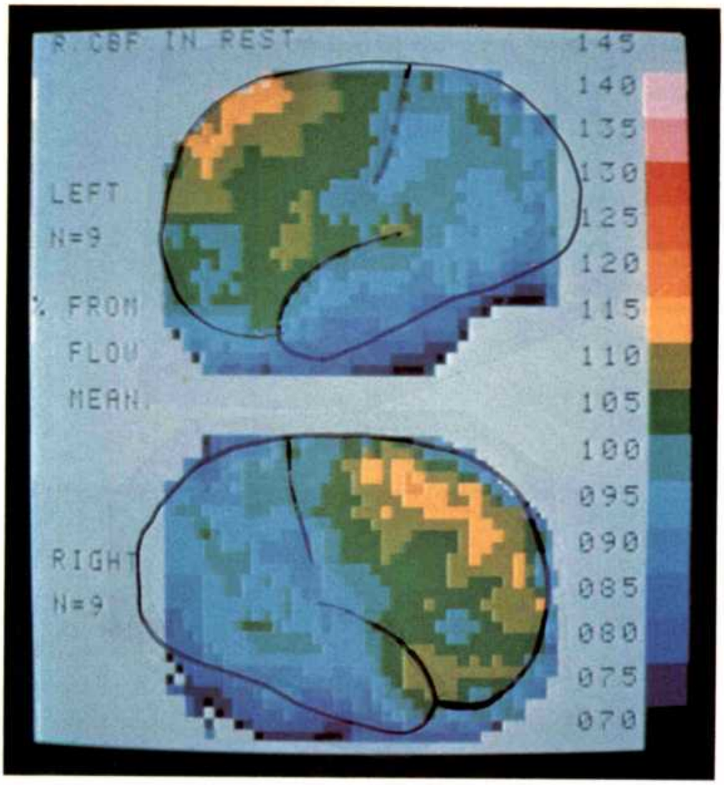


FIG. 3. Average hemispheric flow distribution during rest in subjects tested during automatic speech. Nine left hemispheres (*upper*) and 9 right hemispheres (*lower*).

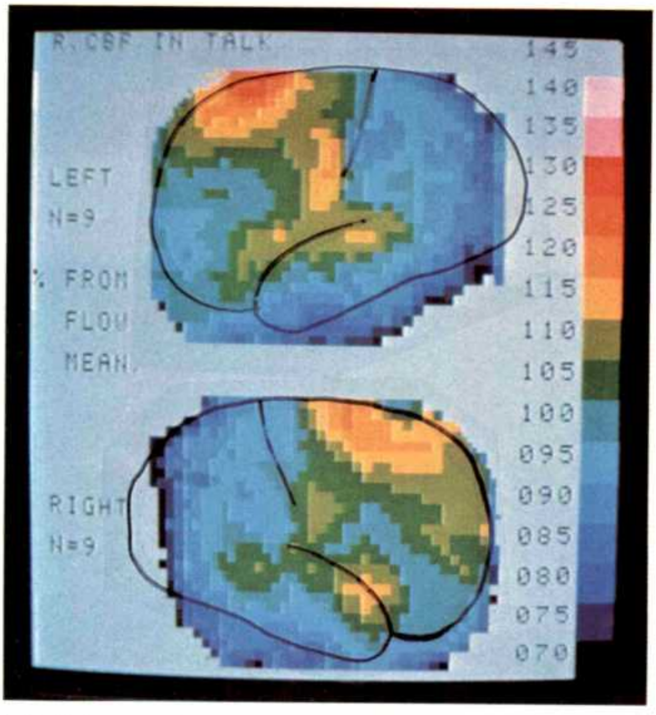


FIG. 4. Average hemispheric flow distribution during automatic speech. The same 9 left hemispheres (*upper*) and 9 right hemispheres (*lower*) as shown in fig. 3.

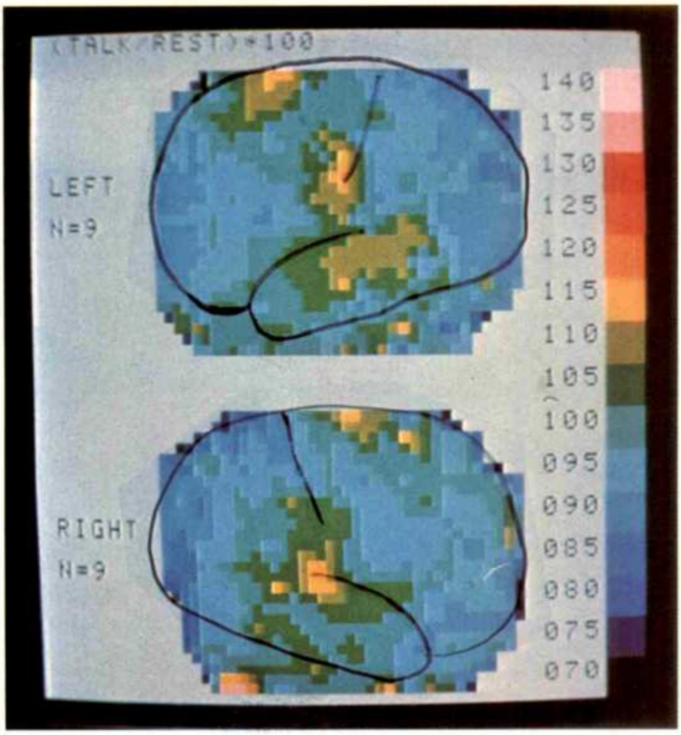


FIG. 5. Average changes in the hemispheric flow distribution from rest to automatic speech. The same 9 left hemispheres and 9 right hemispheres as shown in figs. 3 and 4.

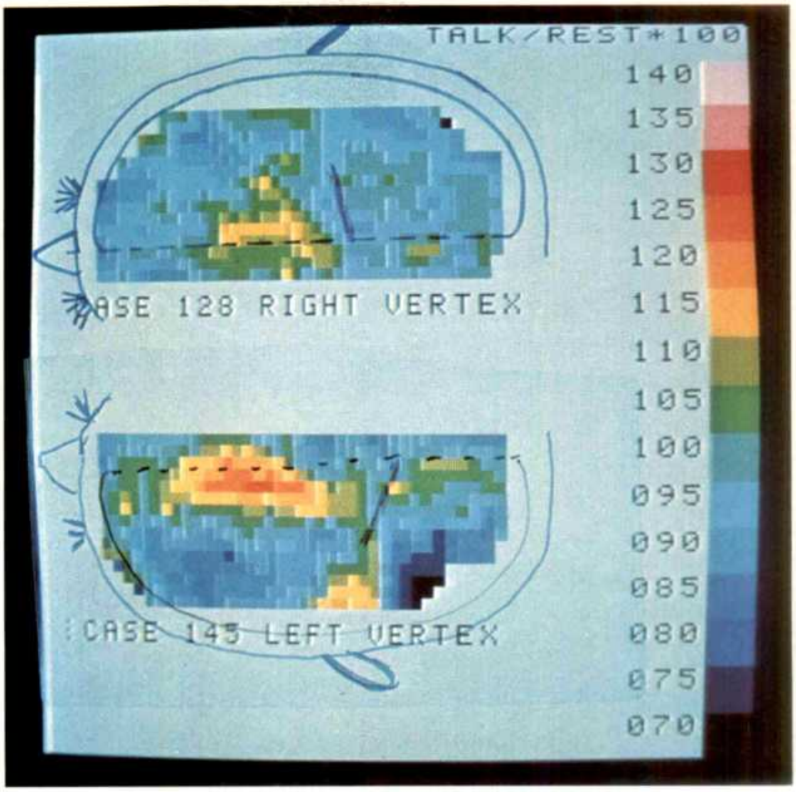


FIG. 6. Vertex view. Changes in the hemispheric flow distribution from rest to automatic speech in one right hemisphere and in one left hemisphere. Increases during automatic speech are seen in the region comprising the supplementary motor area of both hemispheres.

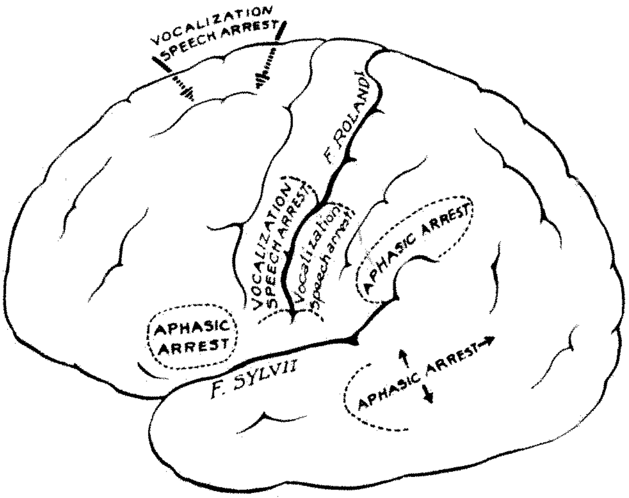

VOCALIZATION SPEECH ARREST
F. ROLANDI
VOCALIZATION SPEECH ARREST
Vocalization speech arrest
APHASIC ARREST
APHASIC ARREST
F. SYLVII
APHASIC ARREST

FIG. 7. Summary of areas in which stimulation may interfere with speech or produce vocalization in the dominant hemisphere (Penfield and Rasmussen, 1949).

Our results from the left hemisphere confirm the findings of Ingvar and Schwartz (1974). Using a 32-detector system they found the blood flow values during automatic speech augmented mainly in a z-like area including the upper frontal, the middle and lower central, and the anterior and middle sylvian regions. The higher spatial resolution of the 254-detector system we use allows a more precise mapping out of the cortical areas involved: the upper pre-motor cortex, comprising the supplementary motor area, the face area of the rolandic region, and the posterior superior temporal region, comprising the temporal auditory area and the auditory speech area of Wernicke. The anterior sylvian region, comprising Broca's area, did not show any increase in rCBF in our study, whereas Ingvar and Schwartz interpreted their pattern of rCBF responses to indicate involvement of this area too.

The most convincing evidence about localization of speech functions has been obtained in neurophysiological studies during neurosurgery. In particular Penfield and his associates have thus outlined for either hemisphere the cortical areas involved in speech (Penfield and Rasmussen, 1949; Penfield and Roberts, 1959). Fig. 7 summarizes the areas in which electrical stimulation interferes with speech or produces vocalization in the dominant hemisphere (Penfield and Rasmussen, 1949). A comparison of their findings with our rCBF maps of the dominant hemisphere (fig. 5, upper part) reveals that our data involve practically the same areas, though the lack of activation of the region comprising the frontal and parietal opercular convolutions in our study is noteworthy. The Broca area at the frontal opercular convolutions in the left hemisphere is a small area as compared to the posterior speech area of Wernicke. The spatial resolution of our measurements may not be fine enough for an increased flow in the Broca area to be detected. Another possible explanation of the apparent lack of response from the Broca and the parietal speech areas is that these areas are also active during 'rest'. It should be noted, however, that during listening to simple words, onomatopœia, without producing speech or during listening to music, we have found localized increases in the frontal and the parietal opercular regions of the left hemisphere (Larsen, Skinhøj and Lassen, to be published).

In the non-dominant hemisphere, Penfield and Rasmussen (1949) found the supplementary motor and the rolandic face area to be involved. However, no response could be elicited from the frontal and parietal opercular convolutions or from the temporal lobe. As illustrated in fig. 5, lower part, we also found activation of the two areas seen by Penfield and Rasmussen. Both are areas that play a role in the motor performance of speech. In addition, on our map the activation also includes the posterior superior temporal region. We interpret this finding as an activation of the right auditory cortex. A simple explanation is that the subjects have been listening to their own voices, using both ears and both temporal auditory areas.

Clinical Aspects

Owing to the consistency of the rCBF response during automatic speech we are now using this test to study the integrity of the cortex in certain clinical syndromes.

With conventional methods, the bilateral cortical connections of the rolandic mouth area and the auditory cortex render it difficult to reveal lesions of these areas in the non-dominant hemisphere. In such cases, particularly in patients with left-sided hemiparesis and no speech abnormalities, the automatic speech test often shows a much wider cortical involvement than suspected clinically or on the basis of EEG, angiography, isotope scan and CT scan.

We have also made preliminary studies of the rCBF pattern in patients with aphasia during attempts to speak (Soh *et al.*, 1978). Such patients constitute a very complex group, particularly with regard to the site of tissue damage. In the 13 patients studied the rCBF pattern showed great abnormalities in the dominant hemisphere. The abnormal rCBF values were not limited to the site of the disease, but revealed cortical dysfunction of areas remote from the primary lesion, probably related to functional derangements of inter-area communications. Thus, in patients with sensory aphasia, as characterized by fluent, but highly abnormal speech, cortical dysfunction was always found in the posterior part of the upper temporal lobe. Patients with motor aphasia, as characterized by inability to speak, but with preserved understanding of spoken and written words, showed dysfunction in the lower part of the rolandic area and the lower part of the pre-motor region (but the Broca area was not found to be consistently involved). In patients with complete lack of all language functions the dysfunction included more widespread cortical areas comprising the posterior temporo-parietal region as well as the lower rolandic area and the adjacent pre-central area.

Our observations demonstrate that the performance of the rather simple task of spoken speech involves activation of both hemispheres. Other aspects of speech should be similarly studied. As mentioned above we have studied the response to a listening test. We also have preliminary results from studies during bi-directional conversation, reading aloud or merely memorizing a text. By this type of systematic survey we expect to show how different constellations of cortical areas are co-operating in performing the different tasks. Conversation, thus, is likely to involve not only the cortical areas of importance for speech, but practically the whole brain, the left as well as the right side. Direct proof of such involvement and even a rough quantitation of the degree of involvement of the different cortical areas are within reach of the functional mapping approach used in this study.

SUMMARY

Regional cerebral blood flow (rCBF) was measured during rest and during an automatic speech test consisting in counting to twenty or reciting the days of the week. The intracarotid ^{133}Xe method was used and rCBF was recorded from 254 regions of one hemisphere: the left in 9 subjects and the right in another 9. All subjects had had carotid angiography for diagnostic purposes, and in all the angiogram, as well as other neuroradiological investigations, were normal.

rCBF measurements during rest revealed no differences between the left and right hemispheres. rCBF measurements during the subsequent automatic speech test revealed an increase of 10 per cent in total hemispheric blood flow in the right hemispheres, whereas no significant change from the preceding measurement during rest was observed in the left hemispheres.

The pattern of flow distribution changed significantly in all the hemispheres. In either side, the flow increased in the upper pre-motor area, probably comprising the supplementary motor area, in the sensorimotor mouth area, and in the auditory area of the temporal lobe. On the left side, however, the pre-motor rCBF increase was more marked and the mouth area was better separated from the auditory area.

In agreement with the classic observations of Penfield and co-workers, we find both hemispheres to be involved during automatic speech. We could not, however, find evidence of activation of Broca's area or of the posterior inferior part of the left parietal lobe.

REFERENCES

BETZ, E. (1975) CBF during emotional stimuli. In: *Brain Work*. Edited by D. H. Ingvar and N. A. Lassen. Copenhagen: Munksgaard, pp. 366–370.

BRANCH, C., MILNER, B. and RASMUSSEN, T. (1964) Intracarotid sodium amytal for the lateralization of cerebral speech dominance: Observations in 123 patients. *Journal of Neurosurgery*, **21**, 399–405.

ELLIOT, F. W. and GRABAU, J. D. (1973) Problems in the electrophysiologic assessment of hemispheric asymmetries during speech. *Electroencephalography and Clinical Neurophysiology*, **35**, 218–221.

GALIN, D. and ORNSTEIN, R. (1972) Lateral specialization of cognitive mode: an EEG study. *Psychophysiology*, **9**, 412–418.

HØEDT-RASMUSSEN, K., SVEINSDOTTIR, E. and LASSEN, N. A. (1966) Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. *Circulation Research*, **18**, 237–247.

—— SKINHØJ, E., PAULSON, O. B., EWALD, J., BJERRUM, J. K., FAHRENKRUG, A. and LASSEN, N. A. (1967) Regional cerebral blood flow in acute apoplexy. The 'luxury perfusion syndrome' of brain tissue. *Archives of Neurology*, **17**, 271–281.

HOMSKAYA, E. D. (1975) Local changes of the functional state of the brain associated with mental activity. In: *Brain Work*. Edited by D. H. Ingvar and N. A. Lassen. Copenhagen: Munksgaard, pp. 424–427.

HOUGAARD, K., OIKAWA, T., SVEINSDOTTIR, E., SKINHØJ, E., INGVAR, D. H. and LASSEN, N. A. (1976) Regional cerebral blood flow in focal cortical epilepsy. *Archives of Neurology*, **33**, 527–535.

INGVAR, D. H. and RISBERG, J. (1967) Increase of regional cerebral blood flow during mental effort in normals and in patients with focal brain disorders. *Experimental Brain Research*, **3**, 195–211.

—— and SCHWARTZ, M. S. (1974) Blood flow patterns induced in the dominant hemisphere by speech and reading. *Brain*, **96**, 274–288.

JACKSON, J. H. (1874) On the nature of the duality of the brain, *Medical Press and Circular*, Vol. 1, pp. 19–43. Reprinted in: *Selected Writings of J. H. Jackson* (1958). Edited by J. Taylor. New York: Basic Books, vol. 2, pp. 129–145.

KANNO, I. and UEMURA, K. (1975) Some experimental errors in calculating regional cerebral blood flow from the intracarotid ^{133}Xe clearance curve. *Stroke*, **6**, 370–375.

KOHLMEYER, K. (1975) Dynamic speech studies by measurement of regional cerebral blood flow in aphasic and non-aphasic cases. In: *Proceedings of the 7th International Symposium on Cerebral Blood Flow and Metabolism.* Edited by M. Harper, B. Jennett, D. Miller and J. Rowan. London: Churchill Livingstone, pp. 14.20–14.21.

LARSEN, B., SKINHØJ, E. and LASSEN, N. A. (1978) Regional cortical blood flow variations in the left and right hemisphere during simple listening. To be published.

LASSEN, N. A. and HØEDT-RASMUSSEN, K. (1966) Human cerebral blood flow measured by two inert gas techniques. Comparisons of the Kety-Schmidt method and the intra-arterial injection method. *Circulation Research*, **19**, 681–694.

MCADAM, D. W. and WHITAKER, H. A. (1971) Language production: Electroencephalographic localization in the normal human brain. *Science*, **172**, 499–502.

MORREL, L. K. and SALAMY, J. G. (1971) Hemispheric asymmetry of electrocortical responses to speech stimuli. *Science*, **174**, 164–166.

OLESEN, J. (1971) Contralateral focal increase of cerebral blood flow in man during arm work. *Brain*, **94**, 635–646.

—— PAULSON, O. B. and LASSEN, N. A. (1971) Regional cerebral blood flow in man determined by the initial slope of the clearance of intra-arterially injected ^{133}Xe. *Stroke*, **2**, 519–539.

PENFIELD, W. and RASMUSSEN, T. (1949) Vocalization and arrest of speech. *Archives of Neurology and Psychiatry*, **61**, 21–27.

—— —— (1950) *The Cerebral Cortex in Man: A Clinical Study of Localization of Function.* New York: MacMillan, pp. 87–108.

—— and ROBERTS, L. (1959) *Speech and Brain Mechanisms.* New Jersey: Princeton University Press, pp. 103–225.

—— and WELCH, K. (1951) The supplementary motor area of the cerebral cortex: a clinical and experimental study. *Archives of Neurology and Psychiatry*, **66**, 209–317.

RAICHLE, M. E., GRUBB, R. L., MOKHTAR, H. G., EICHLING, J. O. and TER-POGOSSIAN, M. M. (1976) Correlation between regional cerebral blood flow and oxidative metabolism. *Archives of Neurology*, **33**, 523–526.

RISBERG, J. and INGVAR, D. H. (1973) Patterns of activation in the grey matter of the dominant hemisphere during memorizing and reasoning. *Brain*, **76**, 737–756.

ROLAND, P. E. and LARSEN, B. (1976) Focal increase of cerebral blood flow during stereognostic testing in man. *Archives of Neurology*, **33**, 551–558.

ROY, C. S. and SHERRINGTON, C. S. (1890) On the regulation of the blood-supply of the brain. *Journal of Physiology*, **11**, 85–108.

SCHMIDT, C. F. (1950) *The Cerebral Circulation in Health and Disease.* Springfield, Illinois: Charles C. Thomas, pp. 37–70.

SOH, K., LARSEN, B., SKINHØJ, E. and LASSEN, N. A. (1978) Regional cerebral blood flow in aphasia. *Archives of Neurology*. In press.

SVEINSDOTTIR, E., TORLÖF, P., RISBERG, J., INGVAR, D. H. and LASSEN, N. A. (1971–72) Monitoring regional cerebral blood flow in normal man with a computer-controlled 32-detector system. *European Neurology*, **6**, 228–233.

—— LARSEN, B., ROMMER, P. and LASSEN, N. A. (1977) A multidetector scintillation camera with 254 channels. *Journal of Nuclear Medicine*, **18**, 168–174.

TALAIRACH, J. and AZIKLA, G. (1967) *Atlas of Stereotaxic Anatomy of the Telencephalon.* Paris: Masson, pp. 52–214.

WADA, J. and RASMUSSEN, T. (1960) Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: experimental and clinical observations. *Journal of Neurosurgery*, **17**, 266–282.

WILKINSON, J. M. S., BULL, J. W. D., DU BOULAY, G. H., MARSHALL, J., RUSSELL, R. W. R. and SYMON, L. (1969) Regional blood flow in the normal cerebral hemisphere. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 367–378.

(*Received July 12, 1977*)

ERSITY COLLEGE LIBRA

Brain (1978), **101**, 211–222

THE NATURAL HISTORY OF INTERMITTENT CLAUDICATION OF THE CAUDA EQUINA

A LONG TERM FOLLOW-UP STUDY

by J. N. BLAU *and* VALENTINE LOGUE

(*From The National Hospitals, Queen Square, WC1 and Maida Vale, W9*)

INTRODUCTION

OUR purpose in this communication is to report on the natural history of the syndrome that we called intermittent claudication of the cauda equina (Blau and Logue, 1961), and to discuss its still disputed pathogenesis.

The subject will not be reviewed in detail, a task ably performed by Jellinger and Neumayer (1972) who collected 120 cases from the world literature. However, a brief point about priorities: credit for the first descriptions must be given to Van Gelderen (1948) who recorded 2 patients, one of whom was successfully decompressed, and to Verbiest (1954, 1955) who annotated the first series of patients. Verbiest (1955) stressed developmental narrowing of the lumbar spinal canal as a major contributory factor but originally considered that the dimensions of the lumbar canal could not be assessed on plain radiographs. Although this has recently been shown to be feasible (Jones and Thomson, 1968), myelography remains the definitive diagnostic procedure.

We reported 6 cases in our earlier communication, since when we have seen a further 16 patients. The long-term follow-up of these 22 patients provides the basis of this report, briefly presented at the Fourteenth International Neurological Congress in Barcelona (Blau and Logue, 1973).

THE PATIENTS

The ages of the patients when seen by us ranged from 32 to 75 years with an average of 58·4 years. The age at onset of symptoms is illustrated in fig. 1. Only one in this series of 22 cases was female: this large male preponderance features in the world literature but remains unexplained (Jellinger and Neumayer, 1972).

The duration of symptoms before referral to a neurological department is illustrated in fig. 2. It is apparent that cases are not being readily recognized. Three modes of presentation were evident in this series.

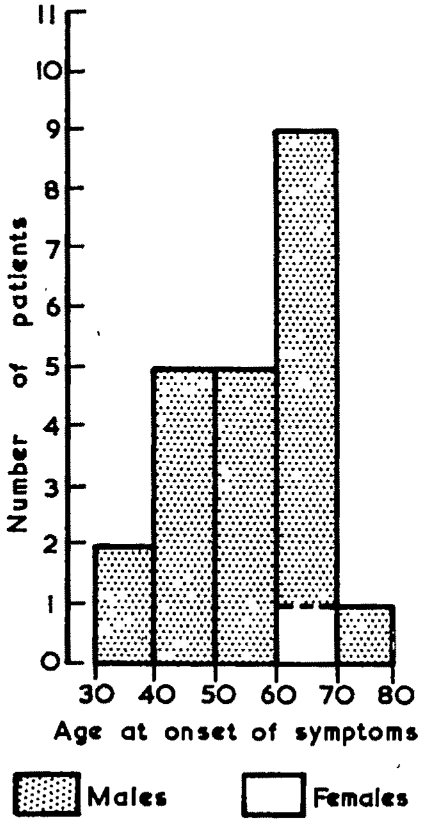


FIG. 1. Patients' age at onset of symptoms.

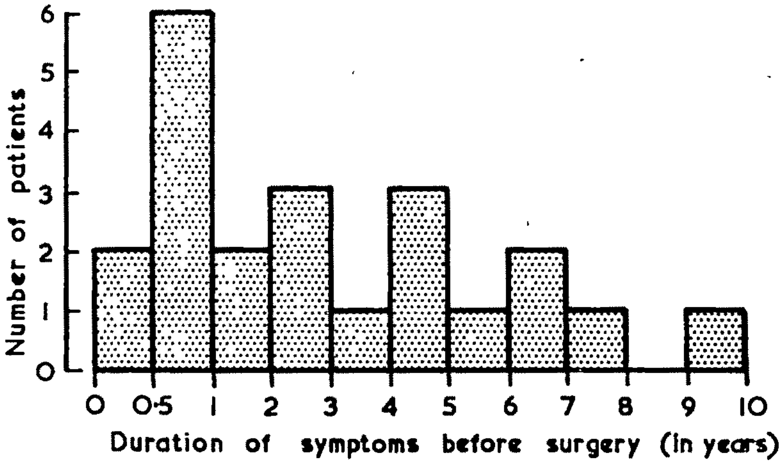


FIG. 2. Intervals between onset of symptoms and operation, in years.

A. 14 Patients

Paræsthesiæ spread along the lumbosacral dermatomes simultaneously or successively in the lower limbs as previously illustrated (Blau and Logue, 1961). These sensations were induced only by activity either (i) after walking a certain distance and relieved by standing, or (ii) after standing for a definitive length of time with relief on sitting down.

B. 5 Patients

Pain in the sciatic distribution provoked by walking or standing but not while sitting or lying.

C. 3 Patients

A mixture of the patterns described under A and B.

In all cases symptoms appeared during a period of activity—usually walking, occasionally while standing but never at rest. When symptoms were at their height 5 patients experienced leg weakness accompanied by fear of falling. In 2 instances urethral sensation was absent when the numbness was maximal.

Physical Signs

Physical signs were remarkably scanty in many instances, even in the presence of disabling symptoms. Thus absence of one or both ankle jerks was the only abnormality in 9 out of 22 patients; in 3 others restricted straight leg raising was the single abnormal physical sign. The remaining 10 subjects had frank evidence of one or more cauda equina root lesions—6 motor, 2 sensory and 2 motor and sensory.

Examination of the lower limbs after sufficient exercise to induce symptoms, the 'exercise test', may assist in diagnosis or management. Initially it may distinguish between neurogenic and vascular claudication, when, in the latter condition, the feet pale and the pedal pulses disappear (De Weese, 1960). In the 10 patients whom we examined after exercise, symptoms of pain or paræsthesiæ were provoked in 4 without change in physical signs. But in 5 others, increased neurological signs were observed: straight leg raising was reduced from 80 to 30 degrees and a foot drop appeared (Case 10); knee jerks became depressed and returned to normal after rest (Cases 1 and 7); knee and ankle jerks increased (Case 12); legs became so weak that the patient nearly fell (Case 19). One patient demonstrated that she could double her walking distance by forward flexion of the trunk (Case 11). Two patients whose claudicating distance was twenty to fifty yards could cycle on a stationary bicycle for distances equivalent to a mile when dyspnœa (Case 19) or aching legs (Case 20) stopped their activity. In one patient, after myelography, symptoms occurred on standing whereas previously intermittent symptoms were brought on by walking a quarter of a mile (Case 18).

Radiology

It has not been possible to trace all the patients' x-rays, particularly those taken more than five years ago, many having been destroyed or lost. Nevertheless, the plain films which have been reviewed reveal considerable pathology: narrowed disc spaces, osteophyte formation, osteoarthritis of apophyseal joints, enlarged laminæ and apposition of apophyseal joints which suggest a narrowed canal in the saggital diameter. The antero-posterior spinal canal diameter is measurable in many instances but the limits are not as well defined as in the cervical region. Furthermore, because the spinal canal may be altered from a rounded to a triangular cavity (Epstein, Epstein and Lavine, 1962), an index attempting to relate the interpedicular distance and antero-posterior canal diameter with the transverse and antero-posterior diameter of the vertebral bodies has been suggested (Jones and Thomson, 1968). However, even with the best plain radiographs, the precise site and extent of the lesion that needs decompression to relieve symptoms is determinable only by myelographic screening. Hence myelography remains the definitive diagnostic procedure. In our series the myodil column was obstructed at the following sites: L3/4 disc level alone, 5 cases; L4/5 disc level alone, 11 cases; two disc levels, 6 cases.

Operative Findings

The spinal canal was narrowed by the following factors, multiple in some instances, in 20 patients who had a laminectomy.

Thickened laminæ	8 cases
Thickened ligamenta flava	11 cases
Hard disc protrusion	7 cases
Soft disc protrusion	10 cases
Narrowed canal in lateral direction	8 cases
Thickened or adherent roots	3 cases

CASE HISTORIES

Three patients required a second operation (Cases 7, 11 and 22) and 2 others were not operated upon (Cases 5 and 17). These case histories will now be described. Because such cases have not previously been recorded we recount the histories in some detail.

Re-operation

Case 7. A 47-year-old man experienced lumbar back pain while digging; this pain lasted six weeks. Five months later, mild exercise provoked bilateral leg pain, initially at the back of the thighs to knee level, but latterly, predominantly in the anterior compartment of the thighs. The pain was accentuated by coughing, sneezing and laughing.

Examination showed tenderness over the lumbar spine. Straight leg raising was 80 degrees bilaterally and the left thigh measured ½ in less than the right. The exercise test showed that after a fifteen-minute walk, he developed lumbar and thigh pains, the left knee jerk became depressed and both quadriceps weak.

On plain x-rays the lumbar disc spaces were minimally narrowed with short, thick pedicles. Attempted lumbar puncture at L3/4 and L4/5 spaces failed but myodil introduced at L2/3 space revealed a narrowed canal and small disc protrusions at L2/3 and L4/5.

At operation, the L2, 3, 4 and upper half of L5 laminæ were thickened (up to 2 cm) and ivory-hard; the diarthrodial joints were only 1½ cm apart, the spinal canal was narrowed and the ligamenta flava thickened. The local joint anatomy caused some restriction of bone decompression at L2 and L3. Both

L5 roots were adherent to a degenerate L4/5 disc which protruded 4 mm into the spinal canal; this disc was removed.

Six months after operation the patient still had back pain and walking five hundred yards gave rise to a sensation of weakness and heaviness in the legs.

He was re-admitted to hospital, when his straight leg raising was 75 degrees bilaterally and the femoral stretch sign positive. A second myelogram showed an almost complete block at L4/5 and considerable obstruction behind the body of L2.

At a second operation, a laminectomy of L1 and L5 was performed, thus the whole of the lumbar spinal canal was decompressed. One year after his second operation, the patient described himself to be symptom-free.

Comment. The restricted L4/5 laminectomy at the first operation was inadequate. The weakness of the quadriceps, the diminished knee jerk after exercise, the unsuccessful lumbar puncture at L3/4 and the initial myelographic findings all provided pointers that the lesion extended higher than the previously decompressed zone. An extensive laminectomy from L1 to L5 resulted in a symptom-free patient and shows the importance of an adequate decompressive procedure.

Case 11. A 69-year-old female physiotherapist developed right-sided sciatica two years earlier. After eighteen months the pain was replaced by a sensation that she likened to a vibrating tuning fork. These paræsthesiæ extended from the soles to the thighs during walking, relieved only partially by sitting but completely by lying down for three minutes. At times, standing for twenty seconds could provoke her symptoms.

Examination showed a tender sacrum; movement of the right hip was painful in all directions but unrestricted; spinal movements were normal and abnormal neurological signs absent. The exercise test revealed that her walking was restricted to twenty-five yards but with her trunk flexed she managed twice this distance before inducing claudication.

Plain x-rays of the lumbar spine showed narrowed disc spaces at all levels with grossly degenerated apophyseal joints at L4/5 and L5/S1. A myelogram demonstrated lateral disc protrusions at L5/S1 and a smaller disc at L4/5.

The laminæ of L1 to L5 were removed, the lower three being grossly hypertrophied and associated with very thick ligamenta flava.

Six months later she was able to walk for half a mile and began to rebuild her physiotherapy practice and one year after operation there was 'no suspicion of vibration'.

Three years later, however, her paræsthesiæ recurred, more readily during walking than while standing. At repeat myelography the myodil column was bilaterally indented and nerve roots appeared swollen at the L4/5 level. A second exploration showed the theca to be compressed laterally by the ligamentum flavum at L5; the laminæ of L4 and L5 were removed more extensively and the L5 pedicles excized to free the canal. Six months later she had made a good recovery but had fallen recently and lost her confidence.

Her symptoms recurred for a third time and she was re-admitted to hospital sixteen months after her second operation.

At this stage the vibration sensation extended from the feet to the ankles after walking thirty to forty yards and even when sitting. Both ankle jerks were now absent but a third myelogram showed lumbar spondylosis without cauda equina compression.

Comment. This patient exemplifies the effect of lumbar flexion in increasing the claudicating distance, presumably by enlarging the lumbar spinal canal, but she illustrates the more difficult problem of patients who have neurological claudication but no compression of the cauda equina roots, an entity that we have encountered several times but for which we have no explanation.

Case 22. A 36-year-old garage owner developed right-sided sciatica, the pain radiating to the ankle after he had lifted a lorry wheel. Three months treatment resolved the pain which, however, recurred periodically. He was advised against having an operation. Seventeen years later, aged 53, his right calf became wasted, the right leg weaker and the outer side of the right leg, sole and toes felt numb intermittently. After a further three years this numbness became continuous; walking one to two hundred yards provoked an additional numb sensation, beginning on the dorsal and plantar aspects of both feet and slowly ascending the lower limbs posteriorly to the buttocks, anteriorly to the groins and at times to the lower abdomen.

At this stage he was admitted to The National Hospital, Maida Vale, where examination showed a normal lumbar lordosis and full spinal movements; straight leg raising induced painless tension at the back of the right thigh. The right calf measured 2½ in less than the left; the right glutei, hamstrings, flexors and extensors of the right toes were weak. Cutaneous sensation was diminished on the outer border of the right foot, the outer two-thirds of the sole and the plantar surface of the toes. The knee jerks were increased, both ankle jerks absent and the plantar responses flexor.

A walk of two hundred yards provoked numbness that began in the right leg and spread to the left. The sensory disturbance disappeared after sitting or lying for a few seconds and recurred after walking another one hundred yards.

Denervation was evident on the electromyogram from the right gastrocnemius and soleus muscles. On plain x-rays there was anterior lipping at L2/3, L4/5 and L5/S1, and slight anterior displacement of L4 on L5. The myelogram revealed a block to the myodil column at the L2/3 disc space and a further block at the L4/5 level. A narrow spinal canal was noted.

At the first operation in 1964 the spines of L2, 3, 4 and 5 were excized. A narrow lumbar canal was found and extremely thick ligamenta flava removed. At L2/3 and L4/5 large buttresses of bone near the apophyseal joints limited the decompression. A very hard L4/5 disc, adherent to the dura, was removed and at the end of the operation the dura bulged backwards.

Within the next three weeks he was walking more confidently for half a mile without precipitating the intermittent dysæsthesiæ. The persistent numbness was also lessening. Three months later he was back at work free from intermittent symptoms; only subjective numbness over L5/S1 and calf wasting remained. He described himself as 'a very different person since my operation'. He continued working without change in his condition when followed up one, three, five and eight years post-operatively.

At the age of 67 years, eleven years after his first operation, he complained of numbness in the right leg and buttock on walking two to three hundred yards, associated at times with numbness of the left foot. During the next twelve months the intermittent numbness radiated from both buttocks to the groins, perineum and genitalia, accompanied by some pain in the groin and his claudicating distance was lessening to one hundred yards before symptoms began. He was still working but in a sedentary post.

He was admitted again in January 1977, when examination revealed wasting of the right calf of 3 in, fasciculation in right gluteus maximus and weakness of all ankle movements (Grade 4). Both knee jerks needed reinforcement to be elicited and the ankle jerks were absent. He had hypæsthesiæ in the distribution of L5 and S1 on the right; the anal reflexes seemed absent but the bulbocavernosus reflexes were present. Straight leg raising was reduced to 75 degrees on each side.

Plain x-rays showed evidence of considerable regrowth of bone along the margins of the previous L2–5 laminectomy, degenerative changes at L2/3 and L4/5, and slight slipping anteriorly of L3 on L4 and L4 on L5. At myelography multiple disc protrusions were found, particularly marked at L2/3, with stenosis at L3 and initial hold up of myodil at L4/5.

At the second operation in February 1977, a solid mass of fibrous tissue was encountered in the midline incorporating scar tissue, ligamenta flava and thickened epidura. Hypertrophied joints approaching the midline were cleared from L2 to L5. The epidural space over S1 was also cleared.

Comment. A lumbar disc at 36 years of age gave rise to intermittent claudication of the cauda equina seventeen years later. His spine was adequately decompressed three years later and was symptom-free for the next eleven years. Then, at the age of 67 years his symptoms recurred, which at operation were shown to be caused by excessive re-formation of fibrous tissue constricting the lumbar theca. Three months after the second operation his walking distance had increased to two miles.

We have not previously encountered or heard of a description of recurrence after a prolonged period of freedom, i.e. a previously adequate decompression.

Cases Not Operated Upon

As far as we know, no cases have been recorded where the diagnosis has been established by myelography but no operation was undertaken. We therefore summarize these two patients' histories which illustrate the duration of symptoms without progression.

Case 5. A 64-year-old physician in general practice (Case 5 in our earlier series) gave a six-month history of dysæsthesiæ of the lower limbs after walking fifty to one hundred yards. On examination straight leg raising was 90 degrees on each side but both ankle jerks were absent. Lumbar spondylosis was evident on plain x-rays and the flow of myodil was halted at L3/4 and L4/5.

Twenty minutes slow walking along the street produced discomfort in the right buttock. After five minutes rest he walked another twenty minutes which provoked tingling on the dorsum of his feet. A further five minutes' rest enabled another twenty minutes of walking with less discomfort than on the two previous occasions.

An operation was therefore deferred, the patient coping with his restricted walking distance. He continued in general practice till aged 68 years. He retired to write his autobiography which was later published. He then returned to work, although his wife stated that latterly he could barely walk round his home; yet he managed to conduct clinics by driving to and from work by car almost to the end of his life, dying of a stroke aged 74 years.

Comment. It seems that this physician's cauda equina syndrome progressed gradually over a ten-year period but in sedentary clinical work and with the aid of the car he was able to cope within his restricted walking distance.

Case 17. The second patient in this group, a 62-year-old credit manager experienced an attack of lumbar pain after gardening one year earlier. Six months later a cramping pain developed in the back of his thighs and calves after walking about one mile. After a further three months his pain also became apparent while lying in bed. Just before his admission to hospital his symptoms were improving.

Examination revealed no spinal or neurological signs but at myelography, the contrast medium was obstructed at L3/4 due to a large disc protrusion in a relatively narrow canal. The exercise test showed that he could walk two thousand yards without pain or discomfort. The patient then decided that he would drive to his office by car and defer an operation. Follow-up at intervals to the present time, seven years after his hospital admission, show no deterioration; his walking and gardening activities remain restricted, lifting heavy objects can provoke back pain and he has periods when he has to sit up in bed at night to relieve his lumbago.

Comment. In this patient there was no progression over a seven-year interval. With a private car and in an executive capacity, the patient was coping within his physical limitations.

In the absence of sphincter disturbance, it seems reasonable not to have operated on these two patients.

FOLLOW-UP

Twenty-one of the 22 patients were traced up to the end of 1973. One patient returned to the Middle East after a laminectomy but repeated attempts to contact him have been unsuccessful. Details of 2 patients who had no operation and 3 others who had two laminectomies, have been related, leaving 16 who had one decompressive laminectomy. This last group was followed up for periods ranging from one to twenty years, the average being seven years.

Totally Free of Claudicating Symptoms (11/16)

Eleven patients returned to work and remained free from symptoms for post-operative periods of twenty*, sixteen*, sixteen*, thirteen*, eight, seven, five, four, three*, two and a half and two years. Those indicated with an asterisk died of unrelated disease (2 from cor pulmonale, one from congestive cardiac failure, one from cerebral hæmorrhage and one from carcinomatosis). The patient with a five-year follow-up period retained numbness of a foot that he had before his operation but like the others in this group, he was completely free from pain or intermittent symptoms.

Symptom-free for a Time then Further Lumbar Spinal Conditions (4/16)

Details about these patients are summarized in Table 1.

TABLE 1. RELAPSED CASES

Case No.	*Years followed*	*Symptom-free years*	*Nature of complication*
19	11	9	Recurrence of paræsthesiæ that restrict his walking. Now aged 71 years.
18	10	9	Recurrence of diffuse backache requiring physiotherapy but able to walk long distances.
4	6	2	Sudden foot drop. Repeat myelogram negative. Hence ? thrombosis of vasovasorum to nerve root.
9	4	½	'Something snapped in back'. Three and a half years later pain on walking.

Condition Unchanged

One patient showed no post-operative improvement.

DISCUSSION

This prolonged follow-up study, which includes cases who did not have a decompressive laminectomy and those who required a second operation, indicates the merit of adequate surgery for this clinical entity. Surgical intervention is not urgent judging by the long interval between the onset of symptoms and the diagnosis being achieved, and by those cases not decompressed. Hence elderly patients seem to be in little danger of developing a complete cauda equina syndrome and may be able to continue sedentary work.

All writers accept that a critical degree of cauda equina root compression must exist in order to produce this syndrome. But the pathogenesis is still disputed, as indicated by the variety of names suggested for the condition: (1) neurogenic intermittent claudication; (2) intermittent ischæmia of the cauda equina; (3) intermittent claudication of the lumbosacral roots; (4) neurological intermittent claudication of spinal or radicular origins; (5) intermittent claudication of neurogenic origin; (6) Verbiest syndrome; (7) lumbar (spinal) canal stenosis.

Opinions differ about (*a*) the factors that narrow the lumbar spinal canal, and (*b*) the mechanism of the intermittent symptoms. We propose to re-examine our original hypothesis that disc degeneration is the main factor narrowing the canal and that the ultimate mechanism of the dysæsthesiæ is vascular insufficiency of the cauda equina roots during activity.

(*a*) *Factors Compressing The Lumbar Theca*

1. The age distribution is comparable with that of cervical spondylosis rather than with a developmental anomaly such as syringomyelia (Brain and Wilkinson, 1958). This fact argues in favour of a degenerative disorder.

2. The remarkable male preponderance, 95 per cent in this and the world series, although unexplained, is not in keeping with an inherited predisposition and contrasts with the genetics of achondroplasia where development of spinal canal stenosis is inherited. We postulate that laminar hypertrophy is acquired secondarily to the greater male musculature. This bony hypertrophy constricts the spinal canal from an oval to a triangular shape (Epstein, Epstein and Lavine, 1962). Interestingly our only female patient was a muscular physiotherapist at the end of a lifetime of hard physical activity.

3. The lumbar roots are compressed posteriorly by the ligamenta flava. We believe that this is a secondary effect of disc degeneration. These ligaments cannot 'hypertrophy' with age but accompanying disc degeneration anteriorly, the laminæ become approximated, causing the ligaments to bulge forwards. Hence when the trunk is flexed the protuberant ligaments become flatter, widening the lumbar theca (Kendall, 1972) and enabling the patient to walk further (Case 11) or cycle without restriction (Cases 19 and 20).

4. It is surprising that intermittent symptoms have not been described in achondroplasia where the spinal canal is congenitally narrow, although we have recently heard of one, case in a series of 4 cases of achondroplasia (Connolly, 1975). One of these had cauda equina symptoms only on exercise, relieved by decompression. But 3 had persistent cauda equina syndromes, hence the inadequacy of the term 'spinal canal stenosis'.

We therefore conclude that the cauda equina roots are compressed anteriorly by a protuberant degenerative disc or a number of discs, posteriorly against the vertebral laminæ or bulging ligamenta flava, and at times laterally between thickened pedicles. Hence the main pathogenetic factor is degenerative as in cervical spondylosis and the developmental size of the canal will play a secondary but important role.

(*b*) *Mechanism of Intermittent Symptoms*

In addition to the critical degree of compression, the intermittent symptoms generated by activity are explicable only on a dynamic basis. Two explanations have been offered—mechanical and vascular.

We postulate that there is a fundamental difference between intermittent claudication arising from the cauda equina and that from a single nerve root (Spanos and Andrew, 1966). In the latter instance the root is compressed extradurally over a spur or disc and the symptoms arise from friction due to movement of the nerve root during walking. The result is pain and not dysæsthesiæ. In the case of the cauda equina there is no movement during walking or standing because the roots run a sinuous course in the lumbar theca. This accounts for the normal straight leg raising in our cases.

We still favour a vascular mechanism to explain the march of paræsthesiæ up or down the lower limbs that occur while walking or standing, a theory with some experimental support (Blau and Rushworth, 1958).

The vascular hypothesis is strengthened by Evans' observations (1964). He found that breathing 12 per cent oxygen reduced the claudicating distance whereas pure oxygen resulted in an unrestricted walking distance. Secondly, in a series of 60 patients with spinal angiomata, 17 had symptoms simulating intermittent claudication during activity in the absence of spinal cord compression (Aminoff and Logue, 1974).

We are, however, unable to account for the two diverse symptomatological patterns—the sensory march and sciatica. Further clinical observations and critical experiments such as hypoxia (Evans, 1964) may illuminate the problem. Experiments on animals with a cauda equina in the spinal canal could be contributory.

In conclusion we accept that the term 'neurogenic claudication' includes intermittent symptoms arising during activity from the spinal cord, for example, in spinal angiomata, from the cauda equina, described here, and from single nerve roots (Spanos and Andrew, 1966). But for the cauda equina syndrome we prefer 'intermittent claudication of the cauda equina' because such a descriptive term does not go beyond the known facts and provides least bias for future research.

SUMMARY

Twenty-two patients with intermittent claudication of the cauda equina have been followed up from one to twenty years. Two patients were not operated upon and their histories are described in detail. The remainder had decompressive laminectomies: 3 of these required further operations and their histories are also described.

The post-operative prognosis of this syndrome was very good, total relief occurring in more than half the patients; the remainder were symptom-free for

a number of years when they developed either recurrence or other symptoms of lumbar disc disease.

The still disputed pathogenesis is discussed, but we favour a vascular mechanism operating in a constricted spinal canal, the latter arising on a degenerative basis.

ACKNOWLEDGEMENTS

We thank colleagues who referred patients and allowed their cases to be included in this series. We also thank Dr. Brian Kendall for help with reviewing the x-rays and the photographic department of the National Hospital, Queen Square, for the illustrations.

REFERENCES

AMINOFF, M. J. and LOGUE, V. (1974) Clinical features of spinal vascular malformations. *Brain*, **97**, 197–210.

BLAU, J. N. and LOGUE, V. (1961) Intermittent claudication of the cauda equina. *Lancet*, **i**, 1081–1086.

—— —— (1973) *Intermittent Claudication of the Cauda Equina.* Amsterdam: Excerpta Medica, International Congress Series, *296*, 103.

—— and RUSHWORTH, G. (1958) Observations on the blood vessels of the spinal cord and their responses to motor activity. *Brain*, **81**, 354–363.

BRAIN, R. and WILKINSON, M. (1958) Cervical arthropathy in syringomyelia, tabes dorsalis and diabetes. *Brain*, **81**, 275–289.

CONNOLLY, R. C. (1975) Personal communication.

DE WEESE, J. A. (1960) Pedal pulses disappearing with exercise. A test for intermittent claudication. *New England Journal of Medicine*, **262**, 1214–1217.

EPSTEIN, J. A., EPSTEIN, B. J. and LAVINE, L. (1962) Nerve root compression associated with narrowing of the lumbar spinal canal. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 165–176.

EVANS, J. G. (1964) Neurogenic intermittent claudication. *British Medical Journal*, **2**, 985–987.

JELLINGER, K. and NEUMAYER, E. (1972) Claudication of the spinal cord and cauda equina. In: *Handbook of Clinical Neurology*. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North Holland, vol. 12, pp. 504–547.

JONES, R. A. C. and THOMSON, J. L. G. (1968) The narrow lumbar canal. A clinical and radiological review. *Journal of Bone and Joint Surgery*, **50B**, 595–605.

KENDALL, B. E. (1972) Radiological investigation of pain referred to the lower limb. *British Journal of Hospital Medicine*, **7**, 500–510.

SPANOS, N. C. and ANDREW, J. (1966) Intermittent claudication and lateral disc protrusions. *Journal of Neurology, Neurosurgery and Psychiatry*, **29**, 273–277.

VAN GELDEREN, C. (1948) Ein orthotisches (lordotisches) Kaudasyndrom. *Acta Psychiatrica et Neurologica, Scandinavica*, **23**, 57–68.

VERBIEST, H. (1954) A radicular syndrome from developmental narrowing of the lumbar vertebral canal. *Journal of Bone and Joint Surgery*, **36B**, 230–237.

—— (1955) Further experiences of the pathological influence of a developmental narrowness of the bony lumbar vertebral canal. *Journal of Bone and Joint Surgery*, **37B**, 576–583.

(*Received July 19, 1977*)

Brain (1978), **101**, 223-250

A CRITICAL APPRAISAL OF POSTERIOR FOSSA SURGERY FOR COMMUNICATING SYRINGOMYELIA

by BERNARD WILLIAMS

(*From the Midland Centre for Neurosurgery and Neurology, Holly Lane, West Midlands B67 7JX*)

INTRODUCTION

THE writings of W. James Gardner (1965, 1973) pointed out that in most cases of syringomyelia a communication exists from the floor of the fourth ventricle to the syrinx cavity. This communication most usually is the central canal, a cavity embryologically continuous with the ventricles of the brain. Gardner indicated that there was no meaningful difference between intracord cavities with an ependymal lining, sometimes called hydromyelia, and cavities which were mostly or partly lined with glial tissue for which the term syringomyelia has been reserved by some authors, Gardner also pointed out that there was commonly an abnormality at the foramen magnum causing some variety of obstruction and opined that blockage of the outlets of the fourth ventricle was important. Williams (1970*a*) has suggested that the blockage of the subarachnoid space at the foramen magnum is more important and that difference in pressure between the head and the spine is more likely to cause filling of the syrinx than funnelling of the 'arterial' pulsations within the CSF pathways which were incriminated by Gardner. These differences in 'venous' pressure are often transient and have been measured and described elsewhere (Williams 1970*b*, 1977*b*), the term 'craniospinal pressure dissociation' has been used to describe this. The dissociation originates most commonly from a valve-like action at the foramen magnum which causes a difference in pressure consequent upon the shifts of CSF caused by the imposition of energy from the venous system. The paradigm of such energy transfer is the cough impulse (Williams, 1976) which has an energy many times greater than that possessed by the pulsations transmitted to CSF by arterial pulsation within the head.

Perhaps the most significant contribution of Gardner and the feature which has led to the widespread acceptance of his ideas, including unfortunately those which are implausible, has been his demonstration that surgical correction of the abnormalities at the foramen magnum commonly produces a remarkable improvement in the clinical condition. Those who have seen such an improvement after operation may experience something close to a religious conversion. Those whose early experience includes disastrous results may on the other hand be dissuaded from further surgery thus failing to produce improvement where it might be obtained. Published reports tend to optimism and include contributions from Newton (1969), Hankinson (1970; 1978), Logue (1971), Vallejo, Portera, Gutierrez del Olmo and Mata (1971), Krayenbühl (1974) and Mohr, Strang, Sambrook and Boddie (1977). Hankinson warned of the hazards of operation upon cases with marked arachnoiditis at the foramen magnum (Appleby, Bradley, Foster, Hankinson and Hudgson, 1969). The recent review of ten years' experience at the Mayo Clinic by Saez, Onofrio and Yanagihara (1976) is more cautionary. Their experience is of sixty cases with 'Arnold-Chiari malformation' rather than specifically syringomyelia as a result of that condition. They note that the presence of syringomyelia constituted the worst prognostic feature for their group and stress the dangers of operating upon cases with arachnoiditis. Of their total of sixty cases almost one-fifth had progressive neurological deterioration at ten years and of patients presenting with central cord disturbance only one-third showed improvement. Banerji and Millar (1974) reported one death out of ten patients operated upon for syringomyelia and only three cases with improvement. Krayenbühl and Benini (1971) advocate valved ventriculo-atrial shunts as primary treatment for communicating syringomyelia despite the complication rates of such procedures and the difficulty of shunting normal sized ventricles or knowing whether such shunts are working. They do not say why they are not satisfied with Gardner's operation except to say that it 'involves certain risks' (Krayenbühl, 1974). Perhaps the greatest condemnation of posterior fossa operations, however, comes from the paucity of articles on the long-term results of such surgery. Gardner, Bell, Poolos, Dohn and Steinberg have published (1977) a description of a new operation for communicating syringomyelia, 'terminal ventriculostomy', without any statement of why they should wish to change from an operation for which optimistic claims were made by Gardner in 1965. Fashions change in surgery often without clear reasons but it would negate a great deal of the thought and energy which has been expended over the past twenty years if posterior fossa operations were to pass into desuetude without an analysis of their defects. It is also difficult to imagine that these operations should have no future if the indications were better understood and the complications more avoidable. For this understanding to be achieved further study into the mechanisms of the disease is necessary and also an appraisal of the dangers and difficulties of posterior fossa surgery as understood at present.

The appended cases have been selected to illustrate the problems of surgery for this condition observed in a series of 41 cases having posterior fossa operations since 1970. Of these cases, 9 of whom had signs of central cord degeneration, 15 showed unequivocal post-operative improvement for a significant time. The post-operative period is too short to justify exhaustive analysis but in addition to some operative mortality and morbidity, some of the cases initially regarded as successful have relapsed months or years after operation. In reviewing these 10 cases some lessons may be learned.

PATIENTS

Case 1

Uncertain ætiology, onset of lumbar syringomyelia aged 22 years. Later respiratory difficulties and restlessness. Tonsillar descent with mild arachnoid adhesion, found dead sixteen hours after operation.

This man was born as the result of a normal labour and was well until the age of 19 years when he was kicked on the occiput. He said that he was never normal after that but was always 'weak'. At the age of 22 years he had pain in the lower abdomen on the right side which persisted for many years. From the age of 26 years he was unable to tell temperature with this part of the abdomen or the right leg. He then suffered from restless nights, having occasional violent movements, particularly kicking; sometimes he had claustrophobia and anxiety. Each night he slept prone with legs flexed at the knee and ankles and the knees not directly underneath him. The head would be turned from side to side and he frequently fell out of bed. He also flexed the knees and hips in other situations and would prefer to squat on a chair rather than sit. He was unable to explain this preference. He was impotent after the age of 33 years and presented at age 37 years because his walking was worsening, he had difficulty in 'getting the legs going' in the morning although he did not have numbness from stretching or compressing peripheral nerves. He did not think that he would be able to walk for much longer and pressed for operation.

On examination he was slightly overweight, the head and neck were of normal dimensions. The thoracic spine was unusually straight with the shoulders almost hanging backwards. The gait was slouching and flat-footed with the head carried slightly forwards. The cranial nerves were normal and there was no nystagmus. The arms were normal including sensation and reflexes. The legs were hypotonic with absent knee and ankle jerks and inert plantar responses. There was an abnormal range of movement at the hips and knees. The power at the hips and knees was almost normal but there was pronounced weakness of both plantar and dorsiflexion at the ankles. There was weakness of the abdominal muscles on the right and the abdominal and cremasteric reflexes were absent on the right.

There was an incomplete dissociated sensory loss on the right from T2 to S1 below which there was sacral sparing. There was depression of temperature sensation over the back of the head and neck and in the middle of the back, the sensory loss spreading over to the left side. He appeared to be dyspnœic at rest on occasions, sometimes using the accessory muscles of respiration. He said that he sometimes felt anxiety over his breathing. He was never observed to have irregular respiration, even when deeply asleep and he was not dyspnœic on exertion.

On investigation his tidal volume and vital capacity were normal. Air encephalography showed a tiny cisterna magna, tonsillar ectopia, failure of the ventricles to fill and a suspicion of a collapsing cord. Ventriculography with iophendylate (Myodil, Pantopaque) showed normal size of the lateral ventricles with a low fourth ventricle from which the contrast medium escaped via Magendie's foramen.

There was concern over the apparent instability of his respiratory system but it was thought that after decompression of the medulla the respiratory difficulties would probably be lessened.

At operation the tonsils were found to be descended and there was slight arachnoiditis. The left tonsil could be elevated and the foramen of Magendie was shown to be potentially patent. Part of that tonsil was sucked out from within its pia, it could then be elevated and its remaining outside membranes sutured to the dura, exposing the left posterior inferior cerebellar artery and leaving the foramen of Magendie widely open. The right tonsil was more adherent to the back of the medulla and there did not seem any necessity to evacuate it. It was sutured to the right side of the dura so that it would not move across the midline. The floor of the fourth ventricle had a funnel-shaped depression at the obex. An enlarged cisterna magna was left behind and the dura closed with a sheet of synthetic substitute. The patient was given mechanical ventilation during the procedure and at the end of the operation began to breathe immediately with a good tidal volume and a normal respiratory pattern. During the following night he was exceedingly restless and in pain because of his attempt to adopt his normal sleeping position. Despite frequent surveillance he was found dead at 5.00 hours the next morning.

Post-mortem examination showed no defect in the operation; there was a communicating syringomyelia maximal in the lumbar region with the communication being present in the usual site. There was no syringobulbia and no abnormality was detected in the medulla apart from a very slight hump below the place where the tonsils had previously laid. The pons and higher brain structures were normal on external and histological examination.

Case 2

Difficult birth, kyphoscoliosis in childhood, syringobulbia at the age of 19 years. Hydrocephalus with a subarachnoid 'pouch' or cyst at the outlet of the midline foramen. Operative correction was followed by protracted debility, adhesions of the tonsils around the operation site, advance of syringobulbia and death after five months.

An only child, born by forceps delivery after a difficult labour, developed kyphoscoliosis in childhood. As a youth he noticed that he was 'rather numb' on the left side of the body. At the age of 19 years he noticed that half of his tongue had atrophied and was fibrillating. After the age of 30 years he complained of aching in the right leg and difficulty with his bladder. In the year preceding admission his legs had been becoming stiff and heavy.

On examination at the age of 49 years, he was an intelligent cheerful man able to do a full day's work. He had a large head, a short neck and marked kyphoscoliosis. There was a dissociated sensory loss over the left side of the face, left arm and upper chest which spread on to the right side to involve the shoulder and the outer part of the arm. There was wasting of the tongue, the left deltoid and the small muscles of the left hand but no deformity of the hands. The legs were spastic with minor posterior column loss.

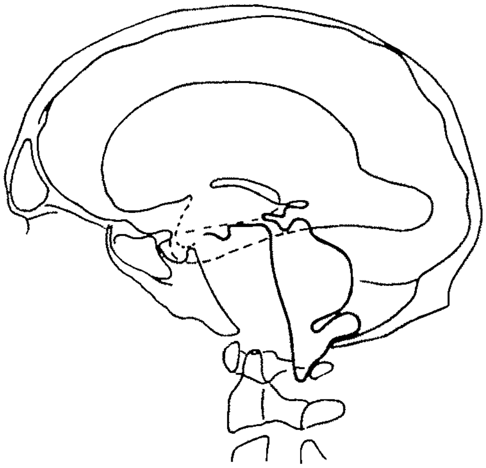


FIG 1, *Case 2*. Outline of bone and ventriculogram to show the extent of the hydrocephalus and the presence of an extraventricular pouch which seemed to have been formed by walling off the outlets of the cisterna magna rather than being due to an imperforate midline foramen.

Investigations confirmed a communicating syringomyelia plus a gross hydrocephalus with a saccular dilatation of the fourth ventricle replacing the cisterna magna. The only opening into this pouch was via the fourth ventricle, the bottom end of which was closed by a membrane below the foramen magnum (fig. 1). At exploration of the posterior fossa the patient was positioned prone so as not to collapse the ventricles. The pouch was outside the cerebellum and the opening into it from the fourth ventricle was about 1 cm wide with the cerebellum to either side. This suggested a patent foramen of Magendie with adhesions forming the pouch rather than a primarily imperforate Magendie. There was no tonsillar descent but the area around was fibrotic with multiple adhesions and the posterior cerebellar arteries were bound down by thickened arachnoid. The bottom part of the pouch was attached to the back of the spinal cord about 1 cm below the normal position of the obex. This was carefully cut away from the back of the cord as well as the area laterally where it was adherent to both the cerebellum and the dura adjacent to the cerebellum. The removal of the bottom edge of the pouch allowed the CSF to escape freely into the spinal subarachnoid spaces.

The cord contained a swelling which passed upwards into the medulla displacing the floor of the fourth ventricle backwards. Aspiration of the cord caused all the swelling to subside. Just above the obex in the midline there was a funnel-shaped opening running downwards. At the end of the procedure muscle was pushed into this opening with intent to block the communication and the wound was closed with a dural substitute.

Initially he seemed well with no increased neurological deficit. He vomited and inhaled later, producing a generalized pneumonitis. He then began to complain of increased generalized weakness and during attempts at walking had hypotensive attacks. Repeated lumbar punctures and ventricular tappings were carried out in order to check that there was no raised pressure and also to clear post-operative blood and exudate from the CSF. One month after operation he suddenly deteriorated with inadequate respiration and dysphagia and required a tracheostomy.

Intracranial pressure remained normal and re-operation on the posterior fossa was carried out five weeks after the first. The cerebellar tonsils were found to be jammed together and adherent to each other in the bony decompression, occluding the outlet of the fourth ventricle. The posterior fossa was closed and a ventriculo-atrial shunt made some improvement but he never regained adequate swallowing or proper use of his limbs. Respiration continued to be inadequate and he died five-and-a-half months after his initial operation.

Case 3

Uncertain ætiology, syringomyelia and syringobulbia at the age of 22 years with progressive deterioration until aged 37 years. Marked hydrocephalus with tonsillar ectopia. High pressure after operation treated by a ventriculo-atrial shunt. Lung abscesses led to death after one month.

This man was born by normal delivery weighing 9½ lbs. His head was thought to have been big in infancy. At the age of two years he fell downstairs and appeared to have 'something wrong with his neck' for a while. He was working as a coal miner at the age of 22 years when he began to suffer from weakness of the left arm, limping in the left leg and hoarseness. He noted that his grip would not relax easily on his tools. He was able to work on the coal face until aged 28 years but his disability continually progressed.

On examination at aged 37 years he was a normally intelligent man, with a large skull, 24½ inches in circumference. He had a normal spine, the left arm was slightly smaller than the right, there was wasting of the scapular muscles on the left and early wasting on the right. The left forearm was spastic, and he could not straighten the fingers. The movements of the left elbow were good. The right arm was almost normal. Both legs were spastic and the muscles of the lower leg were wasted on the left. There was gross nystagmus, principally vertical, on looking to either side. His voice was hoarse and his cough was imperfect. The left forehead was hypoæsthetic, dissociated sensory loss extending over the whole of the left side of the head and the back of the neck, over the shoulder and upper part of the chest, but not affecting the lower arm, forearm and hand. There was dissociated sensory loss on the right side of the shoulder girdle with patchy sensory loss to pin prick and temperature sensation. There was diminution of vibration sense in both legs.

Tomography showed mild basilar invagination. Air encephalography showed hydrocephalus, a small cisterna magna and tonsils descended to the level of the arch of the atlas. The upper part of the cord had collapsed confirming a communicating syrinx. Pressure studies showed pressure dissociation between the head and the spine. Meglumine iocarmate (Dimer X) ventriculography confirmed hydrocephalus; the communication between the fourth ventricle and the syrinx was not outlined.

At operation the opening of the fourth ventricle was occluded over a considerable length and it was not possible to open this widely without sacrificing much of the cerebellar tissue. Both tonsils were evacuated and the membranes sutured upwards and outwards but without obtaining a wide opening into the foramen of Magendie. CSF could however be seen to be escaping freely. It was thought unwise to run the risk of an increased disability from cerebellar distortion by further attempts to open the foramen of Magendie and it was determined to use a ventriculo-atrial shunt if he showed post-operative hydrocephalus. The posterior fossa was therefore closed leaving the dura widely open. Immediately after operation the patient was very well but within two days he became sleepy. There was no increase in his neurological deficit. Pressure recordings of CSF were high.

Placement of a right-sided ventriculo-atrial shunt was carried out four days after the first operation. After this he became pyrexial and began to cough quantities of black sputum. Coughing was difficult because of the tenth nerve palsy and caused him distress. He was suddenly taken ill a week after the shunt with a choking attack due to a release of pus which had been loculated. Tracheostomy produced improvement for a while but then the trachea became infected with Hæmophilus followed later by Pseudomonas. The chest x-rays showed patchy opacities of the lungs which were partly removed by physiotherapy, but recurred in other parts. The sputum became very liquid and antibiotic treatment did not control the organisms. There was an episode of paralytic ileus lasting for several days. He was at this stage showing further neurological deficit, with increasing weakness of the right arm and loss of the ability to swallow. He became very disheartened and progressively weaker. He became suddenly cyanosed and sweaty one month after the initial operation and died shortly afterwards. Post-mortem examination did not disclose any defect of the operative procedures, there was no hæmatoma or wound sepsis. The abdomen, bladder and cardiovascular system were normal. The lungs showed anthracosis and severe bronchopneumonia with abscess formation and purulent pleurisy.

Case 4

Birth injury, back mildly deformed in childhood; syringomyelia symptoms, aged 37 years, progressing until aged 45 years. Minimal hydrocephalus, wide communication from fourth ventricle to syrinx, arachnoiditis. Slight improvement post-operatively followed by high pressure hydrocephalus eight months afterwards and treatment with a ventriculo-atrial shunt.

This lady was born as the first child of a mother less than 5 feet tall, all of whose labours were difficult and one of which was fatal for the child. The labour was protracted and the birth weight was low. Forceps were used and the head was marked. There was feeding difficulty in infancy. Her growth was stunted and her back became rounded. She remained otherwise well until she was 37 years old when she began to notice sensation 'like a coldness' in the left arm and progressive weakness around the shoulder. By the age of 41 years she could not lift the left arm above the head and it was almost useless to her. She became very dependent on the right arm which began to be similarly affected at the age of 43 years. The illness went on to stiffness of both legs and pain in the neck and back of the head. This pain used to come on if she was worried and was not precipitated by exertion or coughing. She was able to work full time as a wages clerk until she was 44 years old when she had a severe influenza-like illness. She had rigors and suffered a fall in the home, she was mentally obfuscated for a while and her neurological state worsened. She seemed to deteriorate further after myelography with the onset of backache, a pricking in the left leg and paræsthesiæ of the left foot and the C6/7 distribution of the right arm.

On examination at the age of 45 years she was mentally normal. She had a short neck, a low hairline and was 4 ft 10 in tall (149 cm) with a hump at the top of the thoracic spine, slightly convex to the right. The thoracic and lumbar spines were unusually straight below that level. The cranial nerves were normal apart from a mild right nerve deafness; there was no nystagmus. The limbs were of equal length. Both arms were held by the side and could not be raised actively although passively there was a full range of movement. There were contractures of the fingers on both sides, the legs were rather stiff and slightly weak although she could walk reasonably well if someone could get her out of her chair or bed. She described herself as being 'like a wooden doll'. There was wasting of the biceps, deltoids, supraspinatus and infraspinatus muscles on both sides and pectoral muscles on the left. There was fasiculation in the left deltoid and hand. There was enough flexion at the right elbow to allow her to feed herself if she could get the elbow on the table, and she could write. All limbs were spastic, tendon jerks were absent from the arms and exaggerated in the legs with upgoing plantar responses.

Sensory testing showed a loss of ability to discriminate between moderate differences in temperature over all the body with the exception of around the mouth and patches on the left leg. The densest loss was over dermatomes C4 to T6 where pain sense was absent and even gross differences in temperature could not be distinguished.

On investigation, x-rays showed a left neuropathic shoulder joint. Air encephalography showed a collapsing cord with fibrous adhesions around prolapsed tonsils. The cisterna magna was obliterated and air failed to enter the ventricles. The anterior cisterns were normal and the subarachnoid space slightly widened. Meglumine iocarmate (Dimer X) ventriculography showed slightly enlarged lateral ventricles with descent of the enlarged fourth and entry of the contrast medium into the syrinx. There was a small blind cavity projecting downwards from the back of the fourth ventricle (fig. 2). Combined intracranial and intraspinal pressure studies showed slight craniospinal dissociation.

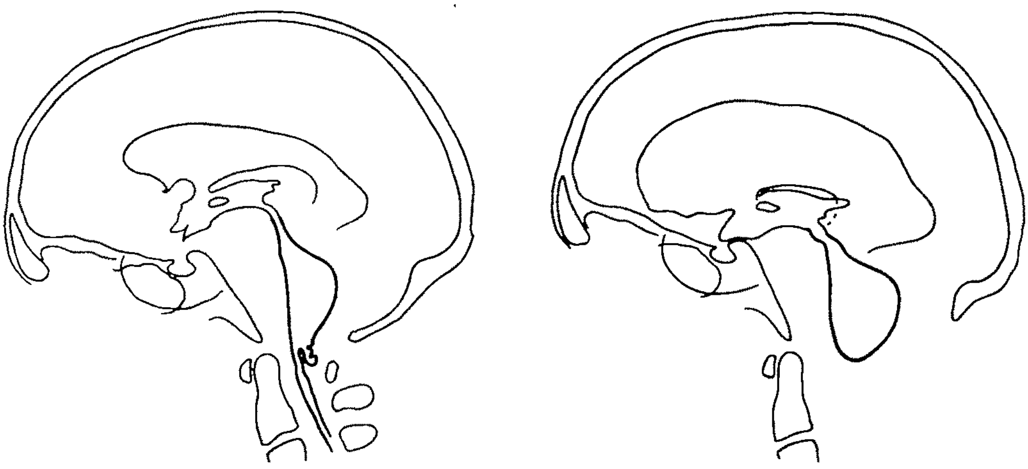


FIG. 2, *Case 4*. The left hand figure shows the pre-operative situation at ventriculography with enlargement of the fourth ventricle only and free passage of contrast medium into the syrinx accompanied by an irregular blockage of the midline foramen. The right hand figure shows the ventriculogram findings eight months after the first operation.

At operation there was no cisterna magna, there was a moderately increased adhesion formation between the dura and the lower part of the cerebellum which at the level of the foramen magnum because a dense band of adhesion binding the tonsils to the overlying arachnoid right across the back of the medulla so that no CSF could pass from the head to the spine posteriorly. There was fibrous tissue which was extending downwards from the left side and completely occluded the subarachnoid space for some centimetres below the foramen magnum.

There was no possibility of lifting the tonsils but since the fourth ventricle was large and close to the surface an opening was made through the vermis about one centimetre above the obex. The opening into the syrinx was blocked by a piece of muscle and the fourth ventricle was held open by stitching the choroid plexus to the dura outside. The space thus created behind the fourth ventricle had an unsatisfactory route for CSF to follow back to the remaining subarachnoid space; it had to flow along the right side of the spinal cord and then up to the basal cisterns anteriorly. Because there was only moderate ventricular dilatation it seemed probable that the foramina of Luschka were patent. The recreated cisterna magna was closed with artificial dura to minimize further adhesion formation. Three millilitres of iophendylate were injected into the syrinx.

Post-operatively she vomited each morning and there was some nystagmus on gaze to the left but otherwise she gained mobility quite well. The left arm was less stiff than pre-operatively and temperature sensation was subjectively improved all over the body; all her pain had gone including the headache and backache which she found to be the most pleasing feature.

Two months after operation her right arm seemed to be worse than pre-operatively. There was some return of backache and headache and the deafness seemed to be worse, particularly on the left side. She also complained of a continuous unpleasant taste in her mouth and tended to faint after straining at stool. The fasiculation had stopped in her muscles and the improvement in sensation to both pin prick and temperature remained. The nystagmus and vomiting had resolved completely and she was cheerful and surprisingly independent.

Eight months after operation she suddenly deteriorated, becoming restless, paranoid and aggressive, unable to walk or feed herself, and with acute retention of urine.

On examination she had bilateral papillœdema, gross spasticity of the legs with bilateral ankle clonus. The arms were as before. Re-screen myelography showed no evidence of arachnoiditis around the thoracic or lumbar spine. The intra-syrinx myodil was unchanged, being down as far as T12 and immobile. Intracranial pressure was raised and ventriculography showed a hydrocephalus with delay in emptying of the fourth ventricle (fig. 2). A ventriculo-atrial shunt was carried out with immediate improvement. After two weeks she could feed herself again, had regained bladder control and was able to stand. Her mental state was quite normal but there was total amnesia for the preceding three or four weeks. She continued to improve and three years after operation she was able to walk about four hundred yards and to write and feed herself as she was before the operation. She retained improved sensation compared with the pre-operative condition, muscle fasiculation had stopped and headaches and vomiting had resolved. The deafness was improved to approximately the pre-operative state. There was still some backache and her overall disability was about the same as before operation.

Case 5

Birth injury, asymmetry of the head and neck, kyphoscoliosis, syringomyelic symptoms aged 21 years, progressive disability with head pain until aged 27 years. No hydrocephalus, cerebellar ectopia—fair result after operation for six months when she had high pressure hydrocephalus treated by a ventriculo-atrial shunt.

This woman was the fourth child of a mother who was in labour for four days, the final stage of the birth being very rapid. All her life she had facial asymmetry with drooping of the right eyelid. She grew stoop-shouldered and from the age of 21 years she noted stiffness and then progressive clawing of the fingers on the right. At the age of 25 years the left hand was similarly affected and the right hand sustained painless burns. When aged 27 years she had symptoms in the legs with sudden attacks of 'giving way' and occasional 'giddiness' as she stopped or moved her head quickly. She also had pain in the left side of the face which radiated into the left shoulder and sometimes across the shoulder girdle to the right side. This was aggravated by sneezing and she also noted that when she yawned the fingers of both hands would forcibly contract and could not be straightened.

On examination she was an anxious slender woman who carried her head tilted backwards and to the right side. The cranial nerves were normal and there was no nystagmus. There was a thoracic kyphoscoliosis concave to the left. There was wasting of the right hand which rested with the fingers flexed, the metacarpophalangeal joints over-extended and the wrist flexed. She could not actively straighten the fingers but there was no rigidity or contracture formation. There was fasiculation in the right scapular muscles and slight wasting and weakness of the left hand and forearm. She had marked depression of temperature and pin prick sensitivity of both arms extending on to the chest wall and up into the neck, the loss was complete to pin prick only along the ulnar borders of the forearms and hands. There was a patchy loss of pin prick sensitivity over the right thigh dermatomes L1/L3. Joint position sense and vibration sense were slightly impaired in the arms and normal in the legs. Tendon jerks were absent from the triceps and those of brachioradialis were depressed. The biceps jerks were present and the tendon jerks at knees and ankles were normal. Abdominal reflexes were depressed but the gluteal and anal reflexes were preserved and the plantar responses flexor.

Combined intracranial and intraspinal pressure recordings showed craniospinal pressure dissociation. X-ray pictures of skull and spine were non-contributory but iophendylate myelography showed a swollen cord and tonsils down as far as the arch of C2. Air myelogram confirmed that the cord collapsed and air did not enter the ventricles. Dimer X ventriculography showed no hydrocephalus, the fourth ventricle was low in position and the contrast medium left it via the foraminæ of Luschka without delay.

At operation the atlas was found to be twisted about 30 degrees from the sagittal plane. This could be corrected by pushing the right lateral mass forward but it persisted in dropping back despite the correct alignment of the head and the atlas in the sagittal plane. The occiput was very flat and thin but there was no shelf of dura and no arachnoiditis. There was a large right tonsil pressed closely against a smaller left tonsil, the two of them forming a smooth tongue of tissue which moulded the back of the medulla.

The right tonsil could be lifted up easily without disturbing the inferior cerebellar artery or the medulla. The right tonsil was incised and partly evacuated with suction, then stitched back to the dura. The left tonsil was small and was left alone. The midline foramen was thus held open. A hypodermic needle was passed through the back of the medulla starting about 1 cm below the obex and was pushed out through the communication (fig. 3). A polyamide 6 suture was pushed through the needle, the needle withdrawn and the upper end of the suture material passed through a small piece of muscle followed by a radio-opaque silastic ball. A silver clip was placed on top of this and the thread pulled down to hold the muscle firmly in the communication. A silver clip was used to hold the bottom end of the thread against the medulla (fig. 3). As this was snugged down there was temporary bradycardia and hypotension.

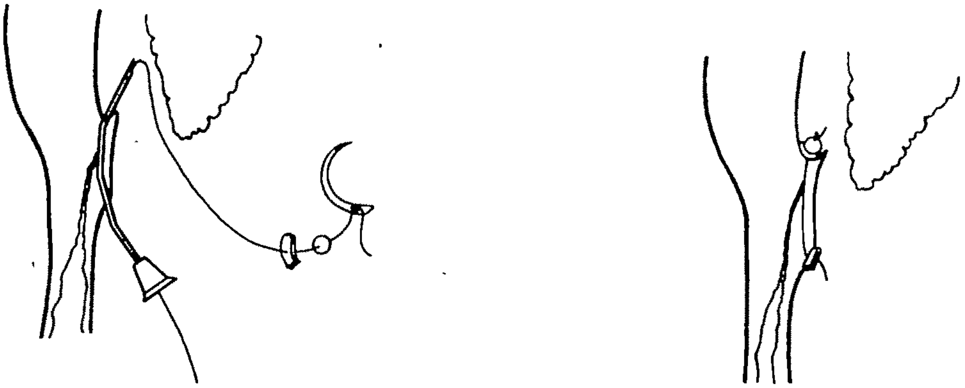


FIG. 3. Method of 'secure blockage' of the communication used in Cases 5, 6 and 9.

Post-operatively the cutaneous sensory abnormalities regressed and were replaced by a slight degree of hyperæsthesia and paræsthesia all over the body. The right hand was more fluent and mobile. Sneezing and yawning produced no ill-effects. On discharge she had very little sensory deficit. Slight deterioration was shown by the left plantar reflex which had become equivocal and the left hand which showed an increased number of errors on testing joint movement sense.

About one month after discharge the occipital headache once more became troublesome and she suffered occasional vomiting. This worsened and five months after operation she had frequent vomiting accompanied by attacks of dizziness and weakness with occasional unsteadiness of gait. Six months after operation she was acutely ill with headache all over the head and severe vomiting.

On examination she was cachectic and dehydrated; the occipital decompression was tight. She was drowsy, unco-operative and denied illness.

Her sensory state was better than before operation but not so good as on discharge. She could tell pin prick in all areas, there was some hyperæsthesia under the right breast. Temperature discrimination was not good in either hand but remained better than before operation. The tendon jerks had returned to the arms and were brisk, the leg jerks were exaggerated and the legs slightly spastic although the plantar responses were flexor. She was very ataxic and could not walk unaided.

Air encephalography showed air in the artificial cisterna magna but no ventricular filling. The tonsils were low and the pattern of the cerebellar folia which had previously been visible was obliterated. The anterior cisterns were smaller than on the previous air study. The diagnosis of hydrocephalus due to re-occlusion of the outlets of the fourth ventricle was confirmed by ventriculography.

A ventriculo-atrial shunt with a Holter low-pressure valve produced immediate improvement. Her vomiting and drowsiness stopped but she became even more aggressive, making imperious demands of her relatives and the nursing staff. Apparently to impress them she tore off all the nails of her right hand with her teeth. Her mental abnormalities gradually resolved and she left hospital in much the same condition as she had first been discharged eight months previously. Her neurological and mental state remained unchanged for two years subsequently but she then developed pain under the right costal margin. Investigations for cholecystitis were negative. Three years after operation her abdominal reflexes have gone as has the right gluteal reflex, and the cutaneous dissociated sensory loss has spread over most of the trunk.

Case 6

Birth injury; sensory symptoms aged 23 years gradually progressing until the age of 33 years. Neck pain, palatal and pharyngeal analgesia. Low fourth ventricle, cerebellar ectopia. Excellent result after operation with almost complete regression of sensory loss. Gradual recurrence of symptoms including early motor signs, not improved by re-operation and blocking of communication.

This girl was born as the first child of a mother who was small and was in labour for four days. Forceps were used and the birth weight was 14 lbs.

She was well until the age of 23 years when she noted that she burned her left hand without feeling pain. She was noted to have nystagmus on left lateral gaze, hyporeflexia of the left arm and dissociated sensory loss.

At the age of 33 years she had severe localized pain behind the left mastoid process. This pain was not precipitated by any known factors, she would bend the head to the left and press it with her hand but this gave only slight relief. She had some difficulty in swallowing food and needed to drink with her meals.

On examination she weighed 17 stone (108 kg), she had scars of burn on the left arm and freckles of the face which crossed the mucous membrane producing some patches of black pigment inside the lips. There was no external abnormality of the skull or spine. The cranial nerves showed sensory loss in the trigeminal distribution on the left with small patches of sparing round the lips and preservation of the corneal response. There was also anæsthesia of the palate and posterior pharyngeal wall on both sides. The sensory loss extended from the trigeminal distribution on the left down to T8 with dense loss to pin prick and temperature. Hypoæsthesia extended to the right side in the mid-cervical dermatomes and it seems probable that the right arm had diminished temperature sensibility. There was some hypoalgesia in the L4/5 distribution on the left. There was a patch of numbness on the left thigh associated with paræsthesiæ which was thought to be due to meralgia paræsthetica. There were no posterior column signs. The left biceps, triceps, brachioradialis tendon and all abdominal reflexes were absent. The left arm had normal tone and normal power to testing but seemed to tire more easily than the right. Tone, reflexes and power were normal elsewhere.

Investigations showed a low intracranial pressure. The cord was of normal size, the cisterna magna was small and the tonsils were herniated. The ventricles did not fill with a spinal air study, iophendylate ventriculography showed no hydrocephalus, the fourth ventricle was low and flattened from behind downwards.

At operation the arch of the atlas was very close to the occiput. The rim of the foramen magnum was thick and upturned. The external appearances of the cord were normal, the cerebellar ectopia was accompanied by a little arachnoid thickening. The medulla and upper cord were rotated, the left-sided structures being further backwards than those on the right and the cerebellar vermis was moved over to the right. The left tonsil was more prolapsed than the right, both could be elevated easily and then it was seen that the fourth ventricle was low and deviated to the right. The inside of both tonsils was evacuated by suction and the remains sutured upwards to the dura. The foramen of Magendie, which had no membrane across it initially, was thus held widely open with the choroid plexus visible in its roof.

After operation there was remarkable improvement. Sensation was observably improved the day after operation and at the time of discharge from hospital she had recovered pin prick sensation over all parts of the body except for some patches on the face. She could tell change in temperature over most of the previously affected area but still made some errors. The sensation returned to the palate and posterior pharynx, she retched when she cleaned her teeth. She thought that this was because she had developed the habit of banging the back of her throat with the toothbrush when it was anæsthetic. The pain in the neck was slightly improved and swallowing seemed to be somewhat better.

One year after operation she had an area of dense sensory loss over the left shoulder and the left side of the neck. The sensation outside this area was apparently normal with temperature being discriminable to a high degree. The abnormal area on the thigh which had been thought to be due to meralgia paræsthesica had disappeared. The left arm became less tired after exertion and the biceps jerk had returned. The only feature which had not been markedly improved by operation was the pain on the left side of the occiput which had recurred and was exactly the same as before operation.

The patient suffered an assault with attempted strangulation some months later, fingers being pressed violently into the occipital decompression. She felt very unwell after this with exacerbation of headache, occasional vomiting, unsteadiness of gait on occasions and transient diplopia. The difficulty in swallowing returned and about one year later she began to notice twitching in the intrinsic muscles of the left hand. The sensory disturbance began to advance again but not in the same pattern as before. It was notably more symmetrical and the palate and pharynx were not involved. She suffered widespread paræsthesiæ and sometimes the legs and feet felt hot.

On examination three years after the first operation she was clearly worse than two years earlier; the legs were slightly stiff with indeterminate plantar responses and re-investigation was initiated.

Air studies showed a large artificial cisterna magna with filling of the ventricles, there was no hydrocephalus. The cord was normal in size but was slightly kinked backwards at the C1/foramen magnum level. Simultaneously pressure recordings were carried out from the ventricles and a lumbar puncture; pressures were low and equalized normally after exertion—that is, no craniospinal pressure dissociation was seen. Thermography showed both legs to be warm, the area around the left big toe being hotter than that on the right.

Re-exploration was decided upon with the intention of injecting myodil into the syrinx. At operation there were adhesions between the tonsils at the site of the suturing at the edges of the dura. This caused the fourth ventricle to be both widely opened and held up so that there was no possibility of the cerebellar tissues slumping into the decompression. There was some adhesion formation between the lateral parts of the medulla and the lateral portions of the spinal canal. This was particularly marked on the left and it looked as though contraction of these adhesions was spreading out the medulla and upper cord at about the level of C1 nerve roots and binding it backwards so that it seemed slightly angulated These adhesions carried a number of blood vessels and were not interfered with. The cord was otherwise normal and no CSF could be aspirated from the syrinx.

The communication was blocked using a polyamide suture inserted as in Case 5 (fig. 3) to hold a piece of muscle in place.

Post-operative x-ray confirmed the correct location of the clips and she was able to return to her normal work. She noticed no benefit from this second operation.

Two years later her condition had progressed with loss of pin prick sensation almost as far as the lips on both sides and progression down the legs to the feet. There was some wasting of the scapular muscles of both sides and fasiculations were present in the small muscles of both hands. There was almost no disability associated with these findings, her major problems being the continuing pain on the left side of the neck and difficulty in temperature discrimination.

Case 7

Multiple deformities in childhood of unknown ætiology, presumed intrauterine. First syringomyelic symptoms at the age of 32 years, progressive deterioration until aged 36 years. Tonsils descended, foramen of Magendie patent, no hydrocephalus or arachnoiditis. Excellent post-operative result, relapse at the age of 38 years with progression of syringomyelic signs and symptoms both motor and sensory. No alleviation after re-operation and blocking of communication.

This man was the youngest of two brothers, born normally into a family with no neurological disorders. The little and ring fingers of both hands were slightly flexed and he had deformed feet at birth. As he grew the abnormalities increased and the left leg and foot became smaller than the right.

He noticed no additional disabilities until aged 32 years when anæsthesia for pain and temperature affected the left hand. The right hand suffered in the same way shortly afterwards. The left hand became markedly weak and stiff the following year. At the age of 34 years he suffered thoraco-lumbar backache. Next year he noticed loss of power in the right hand and also pain in the right occipital region; this was localized behind the mastoid process; he could not identify any causative factors. Also at the same age he had uncertainty of balance and weakness of both legs.

On examination at the age of 36 years he was a cheerful intelligent man with a short neck and a mild kyphoscoliosis, convex to the left. There was a left-sided Horner's syndrome and a coarse nystagmus with a marked rotatory component, the fast element being clockwise. This was exaggerated by leftward and upward gaze. The left grip was strong but the arm was inco-ordinate and spastic; while asleep he drove his finger nails into the palms. The left forearm and infrascapular muscles were wasted. The proximal left leg was weak and there was no movement below the knee. Tendon reflexes were absent in the arms and increased at the knees with an extensor plantar on the right; no response in the left. Sensory testing showed impairment to pin prick over both hands and the neck region from C2 to C4 on both sides. Patchy loss of pin prick sensibility was present over the upper arms and forearms. The ulnar borders of both forearms and hands were completely insensitive. The dermatomes from T2 to T4 were insensitive to temperature. There was a large painless burn scar on the left forearm.

X-ray showed a normal skull and lumbo-sacral spine and a widened cervical spinal canal. On air encephalography the cerebellar tonsils were prolapsed, the cisterna magna was absent, there was good filling of normal-sized ventricles and a collapsing syrinx. Iophendylate ventriculography showed a low fourth ventricle with delayed passage out of the foramen of Magendie. No iophendylate entered the syrinx. Lumbar screening showed no abnormality to explain the longstanding abnormalities of the foot.

At operation the foramen of Magendie was widely open but it was above the band of constriction visible across the back of his prolapsed tonsils. There was no arachnoiditis and the tonsils were evacuated and sutured back to the dura without difficulty. The communication was visible in the floor of the fourth ventricle and its patency was confirmed using sodium fluoresceine but it was not surgically blocked. Iophendylate 1·5 ml was injected into the syrinx.

Post-operatively there was some meningism which was eased by lumbar puncture and aspiration of iophendylate. The intra-syrinx contrast medium descended as far as the conus medullaris and filled two cavities at this level. He rapidly regained full mobility and the left hand became less spastic. The pain in the occipital region was cured. The dissociated sensory loss was diminished around the neck but his gait and overall disability were about the same as before operation.

Seventeen months after operation he had a sudden deterioration in the right arm which was not related to a strain. He noticed that both arms ached after exertion. The gait had grown worse with an increased tendency for the left leg to be 'thrown out' as he walked. There was no recurrence of headache.

On examination he had fasiculation in the left biceps and triceps, the left quadriceps, and in both hands and fingers rather more on the left. The right arm was markedly weaker than before operation.

The nystagmus, Horner's syndrome and reflexes were unchanged. The dissociated sensory loss was confined to the arms and was perhaps more intense than before operation.

Combined cranial and lumbar pressure studies showed a low pressure with no dissociation. Ventriculography and pressure encephalography showed a free connection between the fourth ventricle and an artificial cisterna magna, the cord collapsed.

Re-operation confirmed that the midline foramen was widely open, the cerebellum was held up by sutures and fibrosis around the tonsils. Muscle was pushed into the communication but not stitched.

Post-operatively he was quickly mobile and thought that the left hand and arm were improved. This might well have been a placebo effect and he seemed unchanged at subsequent review.

Four years later he remained unchanged, he could get to work in a modified car and could walk about half a mile. He could do a desk job involving writing but could not tie his shoelaces, comb his hair or manage buttons.

Case 8

Syringomyelic syndrome of unknown ætiology, started aged 49 years with pain; syringobulbia symptoms aged 52 years, rapid progression until the age of 53 years. Tonsillar descent, no hydrocephalus. Poor post-operative course with tremor, ataxia and postural hypotension. Continued to progress after operation.

Born normally as the second child of his mother and with no serious illnesses or injuries, this man was well until the age of 49 years. He then had bouts of pain which started near the midline of the neck and radiated to the left along the shoulder and arm to the fingers. The pain was worse after exertion. Shortly after this the ulnar two fingers of the left hand were noted to be numb, there were paræsthesiæ of the whole limb and the arm became slightly weak. He was disinclined to use the left arm because of pain which became concentrated in the shoulder. At the age of 51 years his voice, which had been hoarse for many years, became worse. At aged 53 years he had stiffness and weakness of both legs and loss of pain and temperature sensibility in the left arm with continuing pain.

On examination he was a normally intelligent man with a normal head and spine. There was a swollen left shoulder joint with limitation of movement and neuropathic changes. Both corneal responses were sluggish, left more affected than the right. There was nystagmus on leftward gaze. The palate deviated to the right, the tongue was fasiculating all over, the voice was hoarse and the cough was rasping and weak, the right vocal cord was paralysed. Sensation was normal over the palate and posterior pharynx. There was a dissociated sensory loss affecting the dermatomes from C2 to T10 on the left and C2 to C4 on the right. There was some posterior column loss involving the left arm.

There was wasting of the left triceps and scapular muscles. Extension of the wrist and fingers on the left was minimally impaired. Both legs were slightly spastic with full power. His gait was almost normal but he could not hop easily. The left biceps and brachioradialis tendon jerks were absent, the left triceps were depressed and the Hoffman's reflex was positive on the right. The tendon jerks were very brisk in the legs but only the left plantar was extensor. The abdominal reflexes and the right cremasteric reflexes were absent, as were the gluteal and anal reflexes.

Investigation showed a low fourth ventricle which filled on air encephalography, tonsillar herniation and slight basilar invagination. There was a collapsing cord.

At operation there was a tight tonsillar herniation and a ridge of dura which was grooving the tonsils opposite a slightly upturned posterior rim to the foramen magnum. The tonsils were raised, partly evacuated and then sutured up to the edge of the dura, the foramen of Magendie was patent with choroid plexus visible in its upper part. The syrinx was injected with 3 ml of iophendylate. The communication from the obex was large and was blocked with a piece of dura which was pushed down the communication but not sutured.

Post-operatively the patient was peculiarly unwell with extreme hoarseness of the voice and inspiratory stridor. There was some dysphagia and dysarthria and a right-sided twelfth nerve weakness. He had a flapping tremor of the outstretched hands and pronounced stiffness. Repeated lumbar punctures were done to ease the meningism but six days after operation he was restless and confused with dyspraxia. Attempts were made to mobilize him twelve days after operation but he collapsed and became cyanosed. Chest radiographs showed the right diaphragm to be raised. The right calf was painful and tender although there was no swelling. Pulmonary embolism was considered and anticoagulants were given. After a further ten days further attempts to mobilize the patient were followed by loss of consciousness; readings of blood pressure were around 60/45. Leg bandages were used but it was five weeks after operation before he was fully ambulant.

He went back to work four months later with no improvement following his operation except that the area of dissociated sensory loss was less.

One year later he was complaining of increasing spasticity in both legs and tingling and numbness of the feet. He had developed an acute swelling of the left elbow due to a neuropathic joint. The pain in the left shoulder was no better and in addition to that he had headaches in the back of the head which were sometimes brought on by lying down but not relieved by anything. Coughing and sneezing made his head spin but produced no other symptoms. He could not hop on the left foot and was unsteady hopping on the right. Both plantar responses were now extensor. The right side of the tongue was very wasted, hoarseness and other lower cranial nerve functions were as before operation. Three years after operation he developed wasting and weakness of intrinsic hand muscles, left more affected than right. He thought that his walking had deteriorated and he had lost weight although he was still able to do a full time job.

Case 9

Probably birth injury, kyphoscoliosis, onset at aged 42 years of relentlessly progressive syringomyelia with episodic features, significantly improved by operation, particularly the spasticity but continuing to deteriorate afterwards.

This man was the son of a short-statured father; his mother was normal and there was no family history of neurological disease. The second child of his mother, he was born after a difficult labour. He was said to have an 'abscess' on the head, to have been very small and was 'expected to die'. He developed normally apart from kyphoscoliosis. He had mild cœliac disease subject to long remissions. At the age of 42 years he lifted a weight and carried it for a short distance and then felt a sudden painful sensation in the left axilla 'like a tearing of the shirt under the armpit'. The arm was sore for a day or two and then became weak. His neurological state deteriorated thereafter. Two years after the onset the left hand was weak. At aged 48 years he coughed vigorously and developed a sudden pain in the left side of the neck spreading up into the head. This symptom recurred, particularly with coughing, over a period of two years and then subsided. At this stage all his arm jerks were present and his plantar responses were flexor. There was fasiculation in the left arm. At aged 52 years he began to notice that the right arm was deteriorating slightly and six months later he sought surgical assistance. He was still able to do clerical work full time.

On examination he was an intelligent man, 5 ft (152 cm) tall, slightly overweight. The head and cervical spine were undeformed but the neck movements were limited in all directions. There was a thoracic kyphoscoliosis concave to the left. The left arm was shorter than the right with wasting of the scapular, arm and forearm muscles. The left arm was spastic, the hand driving the nails into the palm. There was fasiculation in the left triceps, biceps, forearm muscles and thenar emminence. Florid fasiculation was present in the abdomen. The motor function of the right arm was normal to examination. Both legs were mildly spastic.

Tendon reflexes were depressed in the arms, Hoffman's reflex was present in the right hand. Tendon reflexes in the legs were over reactive; the abdominal, cremasteric reflexes and gluteal reflexes were absent. Anal reflexes were present on both sides with bilateral extensor plantars. The gait was slightly broad-based but secure.

Sensory testing showed a dissociated sensory loss almost complete to pin prick and temperature over both arms, it faded into normality over the upper chest but was most dense over the left shoulder and extended up on the left side of the neck and behind the ear in the area in which he had previously suffered pain on coughing.

Iophendylate myelography confirmed an enlarged cord and tonsillar ectopia. Air myelography showed air entering a low fourth ventricle, slight ventricular distension, an indentation across the back of the cisterna magna, level with the foramen magnum, tonsillar ectopia and a collapsing cord.

Meglumine iocarmate ventriculography confirmed a patent foramen of Magendie and filling of the communication.

Operation through a vertical midline incision showed a normal bone structure, there was an abnormally large branch running medially from the right vertebral artery and a ridge of the dura protruded inwards like a shelf corresponding to the indentation seen on the air pictures. There was a groove on the ectopic tonsils caused by impaction against this shelf. The tonsils could be lifted easily and the small fourth ventricle seen. It came lower than had appeared on the x-rays and the obex was several millimetres in depth and almost parallel to the floor of the fourth ventricle so that it formed an unusually marked funnel above the communication. This membraneous obex was divided using microscissors and then a needle was passed through in the way shown in fig. 3 and brought out near the communication. The first placement was inaccurate and needed to be done a second time. A piece of fascia and a 1½ mm silastic ball were used to close the communication. Part of the inside of each tonsil was sucked out and both tonsils were sutured upwards to the dura. A silastic sheet was used to close the dura.

Post-operatively he had retention of urine and some deterioration of gait for a few days. This returned to normal rapidly and was accompanied by improvement in spasticity of the left arm and the plantar responses became flexor. There was some recovery of the sensation in both arms so that the dissociated loss was complete only over the left shoulder and left side of the neck.

He returned to work one month after operation and became fully active. He was playing table tennis some weeks later when he had a sudden pain in the right side of the neck where he had had no previous trouble. He also had some attacks of chest pain. By the age of 53 years the chest and neck pains had lessened and only a residual soreness was present in the right side of the neck. It was not affected by exertion after the initial event. The left arm and the sensory loss continued to be improved compared with the pre-operative condition and his muscle fasiculation was much improved. The right arm was continuing to deteriorate, he fumbled with his keys and had difficulty in writing.

At the age of 55 years, three years after operation, the right arm suddenly deteriorated further with weakness in the shoulder and inability to abduct the arm. About one week after this he had severe pain in the shoulder radiating up into the right side of the neck. There was some spasticity in the right arm, rather more than on the left, but neither were as spastic as the left was before operation. The dissociated sensory loss continued to worsen on the right. The left arm and gait remained as they had since operation, the plantar reflexes had improved once more to produce flexor responses. Neck movements were painful with a good deal of crepitus. The bilateral arm involvement and neck pain later produced such difficulties that he had to give up working. He could not comb his hair, bath himself or hold a pencil.

Case 10

Syringomyelia not proven. Idiopathic tonsillar ectopia associated with arm pain, relieved by a wide decompression at the age of 25 years but replaced by severe headache. Re-investigation at 26 years of age showed massive descent of the cerebellum through the occipital craniotomy.

A woman born as the result of a normal labour was well apart from primary amenorrhœa until aged 21 years when she began to have severe pain in the right forearm and hand which gradually ascended to the shoulder. The pain became more intense and at 24 years of age the right flexor retinaculum was divided without improvement. The right arm became progressively weaker and she developed headaches over the whole head.

At 25 years of age she came under the care of a colleague. She had a slight horizontal nystagmus to the right and weakness of the right arm, most marked in the hand, with blunting of sensation to pin prick and touch over the whole of the right upper limb. Tendon jerks were present and equal on both sides and the plantar responses were flexor.

Iophendylate myelography showed a filling defect at C2 and operation confirmed pronounced cerebellar ectopia. A wide decompression of the posterior fossa was done. The left tonsil was furthest down and was amputated. The upper spinal nerves inclined upwards as they ran laterally and the outlet of the fourth was seen to be lower than normal. The floor of the fourth was not seen, the cord was not visibly cystic but there was a small hump on the medulla. The dura was not closed.

Post-operatively the patient had a good deal of pain in the neck and low back which was eased by lumbar puncture and removal of bloodstained CSF. As this passed off the pain in her arm lessened. The main complaint then became headaches over the vertex and frontal region. They were not felt in the occiput or the neck and did not go into the arm. They were unpredictable, came on at any time of the day and she sometimes woke with them. They sometimes seemed to pulsate in time with her heart but they were not aggravated by straining or changes in posture. They were sometimes made worse by noise. Hard physical work did not seem to cause the headaches and when they stopped this was quick and inexplicable.

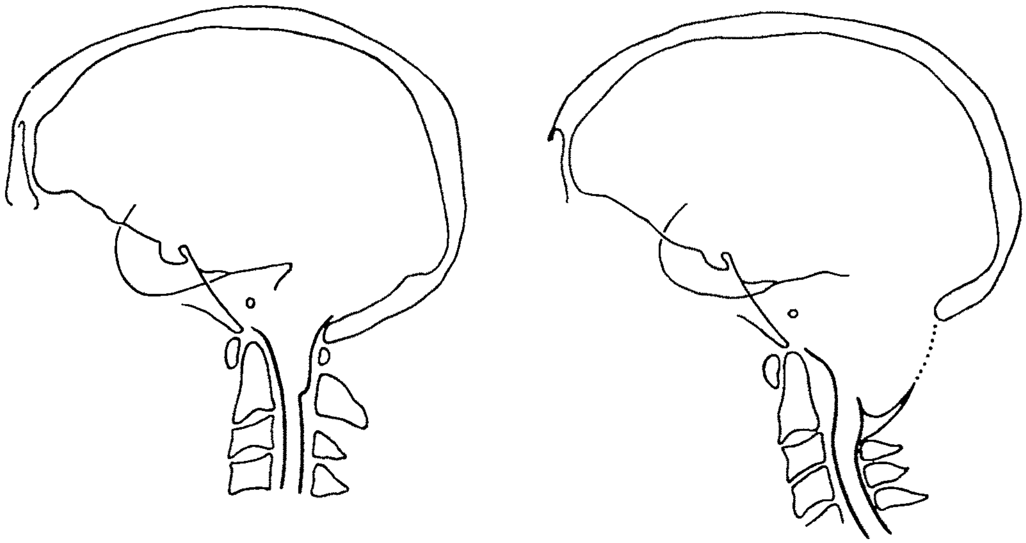


FIG. 4, *Case 10*. Outline of the lower edge of the cerebellum and upper spinal cord as obtained at pre-operative and post-operative air studies. The dotted line indicates the presumed position of the back part of the cerebellum. Note the angulation of the medulla in the post-operative picture suggesting downward displacement of the whole of the stem.

Five months after operation she was unsteady on her feet and tended to veer to the right on walking. On examination she had a marked nystagmus to both sides. The power of the right arm was good. The legs were mildly spastic with an extensor plantar on the left. The left biceps reflex was depressed but the right arm jerks were normal. The epigastric, gluteal and anal superficial reflexes were absent.

Air encephalography showed gross descent of the lower cerebellum and the fourth ventricle. The size of the fourth was somewhat greater than pre-operatively but there was no hydrocephalus (fig. 4).

No operation was advised and the patient continues unchanged after four years.

DISCUSSION

The problems associated with posterior fossa surgery are complex and include consideration of mortality and morbidity after operation and progression of the disease despite operation.

Mortality

The mortality reported by Gardner (1965) was 5 out of 74, that reported by Hankinson (1978) was 3 cases out of 84, Banerji and Millar (1974) one out of 10, Newton (1969) one out of 15, Saez *et al.* (1976) none out of 14. There is in general a paucity of information about the mortality rate. The operative series from which these case reports are taken is of 47 cases, 49 operations, of which 41 were posterior fossa explorations (six re-explorations) and 9 insertions of a valved shunt. The mortality in this series has been 5: Cases 1–3, plus a midbrain glioma (Williams and Timperley, 1977) and a post-operative hæmorrhage after re-exploration. This series therefore almost equals the 15 per cent mortality given by Jefferson (1973). Causes of mortality are various, some, such as air embolism (Newton, 1969), post-operative hæmorrhage or glioma, not being specific to syringomyelia.

One problem is respiratory. Syringobulbia and large cervical enlargement cavities may give respiratory difficulties; problems with clearing the chest were partly responsible for the deaths of Cases 2 and 3. The death of Case 1 suggests that this might have been sleep apnœa. The possibility of cardiac arrest should be considered. No anatomical feature could be found in this case to explain the death. The assumption was made that his cerebellar prolapse and presumed compression caused his unusual posture and restlessness which were a way of keeping the tonsils disengaged from the foramen magnum and that after operation the difficulties would cease. This seems unlikely to have been an error. This example of the syndrome of being 'found dead' is unfortunately not unique (Gardner, 1965; Krayenbühl, 1974; Hankinson, 1978) and since that time all our patients with syringomyelia have had at least twenty hours continuous surveillance post-operatively.

The first three cases were all robust-looking men who had overcome their disabilities with resolution and it is clear that these patients are often more of a risk than they appear.

Morbidity

Increased neurological deficit immediately after operation. Hankinson (1970) comments on the 'surprisingly difficult post-operative period'. Gardner (1965) reported six patients who had worsening of pre-operative symptoms and 'several instances' of bulbar or long tract symptoms, non-existent before operation, which were precipitated by operation. Particularly frail are patients with syringobulbia such as Cases 2, 3 and 8. Deterioration in some degree is not uncommon, including disorders of eye movement, increase in nystagmus (Case 9), increase in ataxia, postural hypotension (Case 8), hiccoughs, vomiting, pyrexia and increased posterior column signs after energetic blockage of the communication (Case 5). Such deterioration is commonly trivial compared with the benefits of posterior fossa decompression.

Exacerbation of hydrocephalus. A proportion of cases have some ventricular enlargement and occasionally, as in Cases 2 and 3, there is marked hydrocephalus. This is due to the same basic pathology as the abnormality of the foramen magnum, most commonly birth injury (Williams, 1977*a*), but also sometimes due to tumour, spina bifida, meningitis or head injury (Williams, 1977*b*). It is tempting to believe that correction of the fourth ventricle abnormality, for instance, by opening the fourth ventricle so that it exits to the spinal subarachnoid space must improve the situation in respect of the hydrocephalus but experience confirms that this is not so. Even patients such as Case 4 with no pre-existing hydrocephalus may become decompensated after operation, presumably due to either inadequate subarachnoid space beyond the foramen magnum combined with the release of blood and proteinous exudate into the CSF pathways, or else fibrosis around the site of operation, possibly combined with repositioning or slumping of the structures such as occurred with Case 2. It is uncertain to what extent hydrocephalus contributed to the death of Case 2. Case 3 might have done better with a more prompt diversion of CSF. In both cases the hydrocephalus was known and the prospect of a shunt kept in mind. Hankinson (1970) reports two cases of hydrocephalus exacerbated after posterior fossa exploration and Newton (1969) had, similarly, two cases requiring a valved shunt. The present policy is to shunt, as initial treatment, all cases with large ventricles, and improvement in the actual syringomyelic symptoms seems to have occurred in such cases rather more often than in cases shunted for syringomyelia who had no hydrocephalus.

Patients 4 and 5 are unusual in the delay which occurred before the onset of hydrocephalus. Post-operative EMI scanning seems likely to be worthwhile in patients whose posterior fossae have been opened.

Progression of foramen magnum abnormalities—arachnoiditis. There is usually some arachnoid thickening around prolapsed tonsils and it is probably artificial to divide the two conditions as though they were separate or had necessarily a different ætiology. Nevertheless, cases with gross arachnoiditis are often identifiable on pneumoencephalography and present a severe problem in management. Dissection is hazardous because structures such as the posterior inferior cerebellar arteries are frequently misplaced and dissection and retraction of the tonsils is impossible without risk of vascular damage. Operation may be followed by increased fibrosis, accentuation of hydrocephalus and progression of neurological disorder. Pre-operative air encephalography/myelography and ventriculography should allow such cases to escape posterior fossa exploration. If gross arachnoiditis is found at operation orderly withdrawal seems commonly to be the best course.

Closure of the dura with a dural substitute might lessen the tendency to adhesion formation (Gardner, 1965).

Gardner has written (1971) opposing interference with the tonsils because of the possibility of provoking further adhesion. If the empty pia can be sutured laterally, holding the midline foramen open, it seems justifiable to make a permanent opening as in Cases 6 and 7. The operative result in these cases was satisfactory in respect of the midline foramen being held open and the surrounding tissues not drooping.

Prolapse through the occipital decompression. If the bone of the occiput is compressing the tonsils then removal of this bone may aggravate the descent of the cerebellum and stem. Even when there is no descent at operation, as in Cases 2 and 4, there may be later slumping of the contents of the posterior fossa and closure of the midline foramen. In Case 10 the slumping was very marked and it seems possible that her headache was due to this. Although she had severe arm pain before operation the head pain was entirely post-operative as was her ataxia and worsened nystagmus. The treatment of a hernia by increasing the size of the hole into which the tissues are jammed is mechanically unsound. It is tempting to use tubing to vent CSF from the ventricles and the subarachnoid space as recommended by Lapras, Poirer, Deruty, Bret and Joyeux (1975). This is only necessary when the tonsils are bound down and the fourth ventricle crowded and small, a situation where any distortion should be avoided. This is difficult and the first consideration is likely to be that of not harming the patient. Small decompressions and valved shunts have much to commend them.

Head and neck pain. Head and neck pain may be present before operation, it is commonly improved, sometimes unchanged, or may be worse after posterior fossa operation. It is a complex subject made so by the usual difficulties of describing and classifying pain, plus the pathological possibilities which must include joint pain, pain from cerebellar prolapse, distortion of nerve roots and pain originating within the spinal cord itself. Several of these causes may be additive in any patient.

Joint pain. The bones of the neck are frequently malaligned (Case 5) and the joints the subject of degenerative disease (Cases 8 and 9). Abnormal fusion of vertebræ are sometimes found and advanced cervical spondylosis, which is often seen, may be partly neuropathic and painful.

Pain from ectopia. It is probable that jamming of the tonsils in the foramen magnum produces distortion of, and traction upon pain sensitive structures (Symonds, 1956; Wolff, 1948). Cough headache may occur during periods of cranio-spinal pressure dissociation and be alleviated after cerebellar decompression and correction of the pressure dissociation. It can resolve spontaneously as it may in non-syringomyelic patients (Symonds, 1956). Cases in which occipital headache is precipitated by exertion and completely relieved after decompression of the foramen magnum are likely to be due to this mechanism. Saez *et al.* (1976) report correction of this symptom as a successful aspect of surgical treatment.

Pain from traction on nerves. Descent of the upper spinal cord and medulla may produce traction on nerves. Tinnitus and deafness is common. The distortion of the upper cervical nerve rootlets and the adhesion of the cord and medulla to the left side of the spinal canal seems the most likely explanation for the persistent and well-localized pain in Case 6. Angulation of the nerves of the upper cervical cord is common with syringomyelic patients and decompression of the posterior fossa is unlikely to benefit such pain; if further descent occurs, as in Case 10, it may be worse.

Pain from within the cord. Tracking of fluid within the cord may cause pain. The injection of saline or CSF into the medulla of the cord appears to cause discomfort in dogs (Williams and Weller, 1973) and patients notice the occurrence of pain in areas supplied by the affected cord. The lower abdominal pain in Case 1 and the pain on the left side of the face in Case 5, aggravated by sneezing, are examples and the backache of Case 4 might have been caused in this way. Sometimes the progression of pain followed by numbness is associated with coughing, sneezing or straining, as in Case 9 (Barnett, Foster and Hudgson, 1973).

Progression of the disease after operation. Even technically excellent results, such as Cases 6 and 7, may be followed by relapse after operation. In these cases re-investigation showed that the surgical objectives had been attained. There was no slump of cerebellar contents, the midline foramen was widely open, and craniospinal dissociation did not occur. The cause of the progression may be vascular changes or further hydrodynamic damage from 'sloshing' of fluid.

Ischæmia. The progressive disruption of spinal cord tissues in syringomyelia is accompanied by gliosis and masses of fibres arranged in annuli around the cord cavities. The suggestion that these are abnormal dates back to Kirch (1927) and Riley (1930). There is little evidence of abnormality other than the profusion of cells, but this gliosis may be associated with vascular insufficiency of the cord (Netsky 1953) and it is possible that this could lead to further gliosis and loss of function.

'Sloshing'. Perhaps more probable is the continuing distending action of fluid within the syrinx. The flaccid nature of the syrinx allows the normal variations of pressure within the CSF of the spinal canal to agitate it into movement. The most convenient pressure events to study are coughs—some have been measured by simultaneous lumbar and cisternal punctures by Williams (1976). During coughing there is a surge of fluid upwards in the greater part of the spine and this can be seen to be imparted to the contents of the syrinx on syringography. As the cough subsides the fluid once more moves caudally with less energy. This surging or sloshing of fluid is almost certainly responsible for the progression of syringomyelia above a cord injury and for the development of syringobulbia (Williams, 1970*b*; Bertrand, 1973). It may indeed be responsible for the greater part of the energy transmission which produces the breakdown of the wall of the syrinx. It may account in part for the principal occurrence of the syrinx in the cervical region. The neatly-rounded upper end of the cavity which is commonly seen, usually at the cervico-medullary junction, would fit better with that explanation than with considerations based upon the water content of grey matter (Gardner 1973), or the proportion of grey matter to white or the outside diameter of the cord at different levels (Williams and Weller, 1973). On theoretical grounds it might be expected that once a syrinx reaches a particular size and the volume of fluid within it increases then it becomes more effective as a 'water hammer'. A given bulk is necessary to collect energy from the subarachnoid space and to deliver in the form of a distending pulsation in another part of the syrinx cavity. It thus seems likely that craniospinal dissociation may be chiefly intrumental in causing a syrinx but that once it is established the sloshing of fluid within the syrinx may be responsible for extending it. Thus although operations for correction of craniospinal dissociation may be partly successful, 'sloshing' may not be lessened and progression can occur which may even pick up speed after all benefit has been gained from the posterior fossa decompression.

Should Posterior Fossa Surgery be Abandoned?

Syringomelia is as unpleasant a disease or rather collection of diseases as any which strikes humanity; its progression is frequently such as to lead to terrible disability and an unpleasant end. The remedy, however, seems to be close to the surgeon's hand. Modern neurosurgery can destroy the choroid plexus, block CSF pathways, shunt CSF through diverse holes and along pipes of varying diameters with valves of differing resistances. Ventricles can be collapsed down to almost nothing, veins could in theory be ligated to raise intracranial venous pressure, massive decompressions can be made in skull or spine or the junction of the two. Syrinxes can be injected with heavy liquids, radioactive liquids and sclerosing liquids. Surely there is a possibility of improving almost all cases if they were detected early and the correct choice could be made?

The surgeon now has three practical options: CSF shunting operations to lower pressure, myelotomy and posterior fossa operations.

Ventricular shunting to lower CSF pressure carries a series of known hazards—infection, thrombo-embolism, blockage of the shunt and over-shunting with collapse of the ventricles. Additional to this, if the shunt is done for a non-hydrocephalic patient how is the patency to be assessed? Repeated CSF punctures to estimate pressures are inaccurate and risk introducing sepsis. Although early reports are optimistic (Krayenbühl, 1974)—early reports generally are, it is possible that in ten years time the literature will contain another nervous silence as surgeons hesitate to reveal the long-term results.

Myelotomy is still a good operation (Love and Olafson, 1966; Saez *et al.*, 1976) despite the risks of damaging the cord. How it works is uncertain. Gardner's variant of 'terminal ventriculostomy' should probably not be attempted unless the cavity can be shown to extend to the filum terminale.

What should the Objectives of Posterior Fossa Operation be?

Correction of cranio-spinal pressure dissociation. This is the most intellectually appealing objective (Williams, 1970*a*, 1974, 1976, 1978). The dissociation can be measured; it impacts the tonsils in the foramen magnum and should be expected to fill the syrinx if the communication is still patent. It seems likely that dissociation is active early in the disease before gliosis is marked or enough fluid builds up in the syrinx to cause significant 'sloshing'. Correction of pressure dissociation can be measured after operation and sometimes clear improvement can be attributed to its correction particularly when there is a symptom such as cough headache which goes immediately.

Unfortunately pressure dissociation is difficult to measure and not all cases can be shown to have it. Correction of the dissociation does not always help and improvement may sometimes occur after operations which do not much alter the dissociation.

Blockage of the communication. Attempts to block the communication by pushing a piece of tissue or thread into the opening of the base of the fourth ventricle have been reported (Gardner, 1965, 1971; Hankinson, 1970, 1978; Saez *et al.*, 1976). The ependyma at this site is smooth and firm wedging produces disturbance such as bradycardia. It thus seems probable that such a plug may come out. Krayenbühl (1974) has opened the top of the syrinx cavity and blocked the communication with muscle inserted from below.

Because of the conviction that correction of craniospinal dissociation was the real objective, no attempt was made, in cases added to this series over some years, to block the communication. Simple decompression of the tonsils without opening the arachnoid has been recommended by Russell (1977). After experience of Cases 6 and 7 it seemed possible that the syrinx was filling passively by seeping of fluid along the communication because the gliosis in the cord wall tended to hold it open and that secure blockage of the communication should be tried (fig. 3). Neither of these patients was helped by the second operation (Case 7 has, however, remained undeteriorated for four years) and subsequent patients have not done better than those in whom the decompression alone has been carried out. Cases 8 and 9 deteriorated after secure blockage.

The literature does not give evidence in favour of blocking of the communication and since secure blockage must increase the risks the question remains unsettled.

Decompression. The tonsils may act as a space-occupying lesion and compress the long tracts at the foramen magnum. Rapid improvement after decompression of the posterior fossa seems to make this likely. In Case 5, for instance, the sensory improvement was notable on the day after operation. If benefit were gained from decompression of the cord, posterior column and pyramidal loss might be expected to be relieved more, or at least as much, as the spinothalamic pathways. Clinical observation commonly does not support this, often the improvement seems to be the greatest in the dissociated sensory loss; although Vallejo *et al.* (1961) report greatest improvement in pyramidal signs and Krayenbühl (1974) noted motor long-tract improvement such as was seen in Cases 7 and 9.

It is recognized that patients, whose only structural lesion seems to be a space-occupying lesion at the foramen magnum, may have symptoms apparently arising within the lower cervical spinal cord (Frenay and Endtz, 1975; Livesen, Ransohoff and Goodgold, 1973; Symonds and Meadows, 1937). It seems likely that most of the cases in these reports had an early communicating syringomyelia which was unproven because the outside diameter of the cord was unaltered.

Improvement of venous drainage. It has been suggested (Blackwood *et al.*, 1963; Taylor and Byrnes, 1974) that the compression of the spinal cord at the foramen magnum causes syringomyelia by interference with venous drainage. This may seem implausible on the basis that the CNS venous system is characterized by widespread anastomoses and alternative valveless channels. It seems impossible to explain a syrinx extending as far as the conus, sometimes even maximal in the lumbosacral region, or to explain syringobulbia on a hypothesis of impaired venous drainage. However, vascular changes secondary to compression by prolapsed tonsils remains a possibility.

Indications for Operation on the Posterior Fossa

Bedbound patients or those confined to wheelchairs seem unsuitable for operation, as do patients with severe associated diseases or advanced age. With these exceptions a sensible view would seem to be that the patients should be operated upon as soon as the condition is diagnosed. Saez *et al.* (1976) advocate early operation to restore normal CSF behaviour. The disease shows a tendency to advance suddenly at times (Cases 4 and 8) even when the early stages have been slow. The sooner the operation is done, the better the condition in which the patients are to withstand the risks, and the better the quality of the patient's remaining life.

These obvious considerations are offset by reviewing the case histories herein. Although some of the cases appear to hold their ground very well after operation the proportion is unknown. A longer follow-up may indicate a more pessimistic result and the indications for posterior fossa operation may become more refined with the passage of time.

Re-operation on the posterior fossa has not produced improvement in any of these cases and seems rarely indicated. The result in Case 2 was only to reveal a degree of slump and re-obstruction of the fourth ventricle; if it had been corrected at the second operation then the result would have been destruction of more cerebellar tissue without certain correction of the hydrocephalus. A valved shunt seemed more sensible and was successful in Cases 4 and 5. Re-exploration of Cases 6 and 7 only confirmed what investigations had shown and no useful improvement seemed to result. Two other re-explorations showed only a situation even more hopelessly adherent and fibrosed than at initial operation. One of these cases died from post-operative hæmorrhage.

The degree of slump in Case 10 was so gross that no useful surgical treatment could be planned.

In general, if the posterior fossa cannot be well reconstructed at the first attempt, then the situation is likely to be worse on the second occasion and if blocking of the communication, injection of iophendylate, or insertion of a tube is the surgeon's policy, it would seem best to carry out such manipulations at the first attempt.

Other Operative Possibilities

Lessening of 'sloshing'. There are two possibilities of lessening 'sloshing': mechanical interference with the cord, and altering the fluid dynamics of the spinal cavity by changing the capacitance of the neuraxis as a whole.

Mechanical interference with the cord. Having a cord flat and empty must be the preferred state. However, blockage of the communication cannot be expected to produce this; backwaters of CSF lie about in the tissue of the neuraxis away from sources of replenishment, yet are not absorbed. It has been suggested that the lining of syringomyelic cavities may secrete fluid (Barnett *et al.*, 1973; Lichtenstein, 1949) and this cannot be disproven. Drainage of the spinal cavity by myelotomy cannot be expected to flatten a flaccid syrinx cavity; a myelotomy might just as well allow the syrinx to fill. Could the good results noted after operation of myelotomy be due to adhesion formation and interference with 'sloshing' by implanted tubes, wires, and so on? Gardner *et al.*'s (1977) recently-advocated operation of cutting off the filum terminale to make a myelotomy may work in the same way. Perhaps it is significant that the most successful surgical operation for syringomyelia in communication with the CSF pathways is gross mechanical interference with the cord such as can be practised on syringomyelia above paraplegia (Barnett *et al.*, 1973).

Blockage of the inside of the syrinx may be considered. The infusion of heavy viscous fluid into the syrinx in the form of iophendylate (Myodil, Pantopaque) is tempting. Such a fluid must surely damp down 'sloshing'. Although good reports have come from Michelson (1970), no case has been observed in this series in which instillation of Myodil appeared either to help or to cause an adverse result. Myelotomy and introduction of muscle or sponge into the cavity or instillation of a sclerosing agent, for example, a suspension of a foreign protein such as milk, might be considered. The surgeon would have to be sure that inflammation, possibly with exudation of fluid and eventually further gliosis, could not lead to further loss of function. Questions such as these demand the development of an adequate animal model before they can be investigated, and in the present state of knowledge a surgeon would be bold to attempt such measures.

Changing capacitance of the neuraxis. Capacitance of the neuraxis can be changed by, for instance, the insertion of a ventriculo-atrial shunt; or by decompressive operation. If the CSF pressure is lowered then the venous system becomes proportionately more distended. This pre-fills the veins which transmit abdomino-thoracic pressure to the CSF pathways. These veins thereafter cannot accommodate such a large influx of fluid as they could when they were in their previous, partly collapsed, state. Proof of this mechanism is not available in humans but a model has demonstrated these phenomena (Williams, 1974). If the energy transmission from veins to CSF is lessened then energy imposition upon the syrinx may be lessened, both during cranio-spinal dissociation and 'sloshing' (Williams, 1974, 1976).

It is a sobering thought for the proponents of ingenious operations that the good results from decompression of the posterior fossa, blocking of the top and bottom of the communication, myelotomy, ventriculo-atrial shunting and Gardner's terminal ventriculostomy might all be largely due to alteration of capacitance.

CONCLUSIONS

Posterior fossa decompression operations offer considerable prospects of improvement for sufferers from communicating syringomyelia. The mechanisms underlying this improvement are obscure.

There is no adequate evidence to prove that blockage of the communication is helpful in reversing or arresting the progress of the disease.

There is a considerable mortality from posterior fossa operations, five patients in this series of forty-one operations.

There is a morbidity associated with posterior fossa operations which is usually transitory but includes the development of hydrocephalus even months after the procedure.

In addition to the obvious surgical hazards associated with age, respiratory symptoms, generalized muscular weakness, arterial hypertension or postural hypotension and so on, mortality and morbidity are particularly associated with pre-existing hydrocephalus, syringobulbia and arachnoiditis.

Patients with hydrocephalus could reasonably be treated with a valved ventriculo-atrial shunt in the first instance.

Demonstration of craniospinal pressure dissociation does not provide a certain indication for posterior fossa surgery.

Decompression of the posterior fossa may have to be limited by the consideration that the cerebellum may continue to slump and become impacted within the bone defect as it previously was in the foramen magnum.

Even when craniospinal pressure dissociation is corrected and the medulla is decompressed the disease may continue to advance at a rate similar to that before operation.

Advancement of knowledge in this disease is to be encouraged and may be expected to yield continually improving results.

SUMMARY

The demonstration of the association between abnormalities of the foramen magnum and the commonest form of syringomyelia has led to advances in the understanding of this disease. The association between the blockage at the foramen magnum and a communication from the cerebrospinal fluid pathways with a syrinx has produced surgical attempts at correction often with good results in the short term. The exact mechanisms of syringomyelia are unknown, but craniospinal pressure dissociation seems likely to be important in the development and progression of the syrinx and correction of the foramen magnum abnormalities may produce benefit by lessening this dissociation.

Other benefits may come from blocking the communication, altering the capacitance of the neuraxis or decompression of impacted tonsils relieving direct pressure upon the underlying cord and its blood supply.

There are disadvantages of posterior fossa operation. Complications include sudden respiratory arrest, exacerbation of hydrocephalus, aggravation of cerebellar, brain-stem and spinal cord neurological signs, postural hypotension, abnormal descent of the cerebellum, nuchal and occipital headache; also the disease sometimes progresses significantly even though the posterior fossa situation has been refashioned.

On occasions the disease is unimproved by posterior fossa operation and even without operation, syringomyelia sometimes remains clinically static for many years. Illustrative clinical histories are given and it is suggested that improvements are required in the pre-operative assessment of patients with communicating syringomyelia in conjunction with an improved understanding of the mechanisms which produce and extend the cavitation.

ACKNOWLEDGEMENTS

Secretarial assistance has been provided by the locally organized Research Scheme of the West Midlands Regional Health Authority.

REFERENCES

APPLEBY, A., BRADLEY, W. G., FOSTER, J. B., HANKINSON, J. and HUDGSON, P. (1969) Syringomyelia due to chronic arachnoiditis at the foramen magnum. *Journal of the Neurological Sciences*, **8**, 451–464.

BANERJI, N. K. and MILLAR, J. H. D. (1974) Chiari malformation presenting in adult life—its relationship to syringomyelia. *Brain*, **97**, 157–168.

BARNETT, H. J. M., FOSTER, J. B. and HUDGSON, P. (1973) *Syringomyelia*. London: W. B. Saunders.

BERTRAND, G. E. (1973) Dynamic factors in the evaluation of syringomyelia and syringobulbia. In: *Clinical Neurosurgery*. Baltimore: Williams and Wilkins, Vol. 20, pp. 322–333.

BLACKWOOD, W., MCMENEMY, W. H., MEYER, A., NORMAN, R. M. and RUSSELL, D. S. (1963) In: *Greenfield's Neuropathology*. Edited by W. Blackwood London· Arnold, pp. 331–337.

FRENAY, J. and ENDTZ, L. J. (1975) Considérations sur la pathogénie de l'astéréognosis et de l'amyotrophie de la main dans les méningiomes cervicaux supérieurs. *Revue Neurologique*, **131**, 139-142.

GARDNER, W. J. (1965) Hydrodynamic mechanisms of syringomyelia: its relationship to myelocoele. *Journal of Neurology, Neurosurgery and Psychiatry*, **28**, 247-259.

—— (1971) Personal communication.

—— (1973) *The Dysraphic States—from Syringomyelia to Anencephaly*. Amsterdam: Excerpta Medica.

—— BELL, H. S., POOLOS, P. N., DOHN, D. F. and STEINBERG, M. (1977) Terminal ventriculostomy for syringomyelia. *Journal of Neurosurgery*, **46**, 609-617.

HANKINSON, J. (1970) Syringomyelia and the surgeon. In: *Modern Trends in Neurology*, 5th Edition. Edited by D. Williams. London: Butterworths, pp. 127-148.

—— (1978) The surgical treatment of syringomyelia. In: *Advances and Technical Standards in Neurosurgery*. Vol. 5. Edited by H. Krayenbühl. Vienna: Springer Verlag. In press.

JEFFERSON, M. (1973) Syringomyelia. *Practitioner*, **211**, 310-315.

KIRCH, E. (1927) Zur pathogenese der syringomyelie. *Verhandlungen der Deutschen Pathologischen Gesellschaft*, **221**, 221-226.

KRAYENBUHL, H. (1974) Evaluation of the different surgical approaches in the treatment of syringomyelia. *Clinical Neurology and Neurosurgery*, **77**, 110-128.

—— and BENINI, A. (1971) A new surgical approach in the treatment of hydromyelia and syringomyelia. The embryologic basis and the first results. *Journal of the Royal College of Surgeons of Edinburgh*, **16**, 147-161.

LAPRAS, C., POIRIER, N., DERUTY, R., BRET, P. and JOYEUX, O. (1975) Le catheterisme de l'aqueduc de Sylvius. Sa place actuelle dans le treatment chirurgical des stenoses de l'aqueduc de Sylvius des tumeurs de la F.C.P. et de la syringomyelie. *Neurochirurgie*, **21**, 101-109.

LICHTENSTEIN, B. W. (1949) Syringomyelia. In: *Textbook of Neuropathology*. London. Saunders.

LIVESON, J. A., RANSOHOFF, J. and GOODGOLD, J. (1973) Electromyographic studies in a case of foramen magnum meningioma. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 561-564.

LOGUE, V. (1971) Fourteenth Crookshank Lecture. Syringomyelia: A radio diagnostic and radio therapeutic saga. *Clinical Radiology*, **22**, 2-16.

LOVE, J. G. and OLAFSON, R. A. (1966) Syringomyelia: A look at surgical therapy. *Journal of Neurosurgery*, **24**, 714-718.

MICHELSON, W. J. (1970) Personal communication.

MOHR, P. D., STRANG, F. A., SAMBROOK, M. A. and BODDIE, H. G. (1977) The clinical and surgical features in 40 patients with primary cerebellar ectopia (adult Chiari malformation). *Quarterly Journal of Medicine*, **46**, 85-96.

NETSKY, M. G. (1953) Syringomyelia, a clinico-pathologic study. *Archives of Neurology and Psychiatry*, **70**, 741-777.

NEWTON, E. J. (1969) Syringomyelia as a manifestation of defective fourth ventricular drainage. *Annals of the Royal College of Surgeons of England*, **44**, 199-213.

RILEY, H. A. (1930) Syringomyelia or myelodysplasia. *Journal of Nervous and Mental Disease*, **72**, 1-27.

RUSSELL, J. A. (1977) Personal communication.

SAEZ, R. J., ONOFRIO, B. M. and YANAGIHARA, T. (1976) Experience with Arnold-Chiari malformation, 1960 to 1970. *Journal of Neurosurgery*, **45**, 416-422.

SYMONDS, C. P. (1956) Cough headache. *Brain*, **79**, 557-568.

—— and MEADOWS, S. P. (1937) Compression of the spinal cord in the neighbourhood of the foramen magnum. *Brain*, **60**, 52-84.

TAYLOR, A. R. and BYRNES, D. P. (1974) Foramen magnum and high cervical cord compression. *Brain*, **97**, 472-480.

VALLEJO, J. R., PORTERA, A., GUTIERREZ DEL OLMO, M. C. and MATA, P. (1971) Revision del concepto de siringomielia con especial referencia al tipo 'communicante' por defecto en el drenaje del cuarto ventriculo. *Revista Clinica Espanola*, **120**, 363-368.

WILLIAMS, B. (1970*a*) Current concepts of syringomyelia. *British Journal of Hospital Medicine*, **4**, 331-342.

—— (1970*b*) The distending force in the production of communicating syringomyelia. *Lancet*, **2**, 41-42.

—— (1974) A Demonstration Analogue for Ventricular and Intraspinal Dynamics (DAVID). *Journal of the Neurological Sciences*, **23**, 445-461.

—— (1976) Cerebrospinal fluid pressure changes in response to coughing. *Brain*, **99**, 331-346.

—— (1977*a*) Difficult labour as a cause of communicating syringomyelia. *Lancet*, **2**, 50-53.

—— (1977*b*) On the pathogenesis of the Chiari malformation. *Zeitschrift für Kinderchirurgie und Grenzegebiete*, **22**, 533-553.

—— and TIMPERLEY, W. R. (1977) Three cases of communicating syringomyelia secondary to midbrain gliomas. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 80-88.

—— and WELLER, R. O. (1973) Syringomyelia produced by intramedullary fluid injection in dogs. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 467-477.

WOLFF, H. G. (1948) *Headache and Other Head Pain*. London and New York: Oxford University Press.

(*Received September 27, 1977*)

Brain (1978), **101**, 251-283

THE CORTICOPONTINE PROJECTION IN THE RHESUS MONKEY

ORIGIN AND PRINCIPLES OF ORGANIZATION

by P. BRODAL[1]

(*From the Department of Human Anatomy, South Parks Road, Oxford OX1 3QX*)

INTRODUCTION

CEREBELLAR lesions in man lead, among other symptoms, to 'abnormalities of rate, regularity and force of voluntary movements' (Holmes, 1939). On the basis of careful studies of patients with cerebellar disorders, Holmes concluded that this disturbance of voluntary movement is due to a disruption of the connections between the cerebellum and the cerebral cortex. He also based his conclusion on the fact that in man, the cerebellar hemispheres make up most of the cerebellum and, as is well known, this part is mainly connected with the cerebral cortex. During the evolution of increasingly versatile skilled movements, the sizes of the cerebral and cerebellar hemispheres increase in parallel. Therefore, in order to understand the function and dysfunction of the cerebellum in man, it is important to obtain experimental data in animals having well developed cerebellar hemispheres, that is, in primates. Indeed, the cerebellar role in the control of movement in primates has recently attracted much interest from physiologists (*see* Evarts and Thach, 1969; Allen and Tsukhara, 1974). For example, by cooling the dentate nucleus, which receives the Purkinje cell axons from the cerebellar hemispheres, disturbances of voluntary movements very similar to those seen in man are produced (Conrad and Brooks, 1974). A thorough knowledge of the anatomical organization of the pathways involved is of importance for a full evaluation of the physiological results, but so far detailed anatomical studies on these pathways have been performed only in the cat. However, due to the moderate development of the cerebral cortex and the cerebellar hemispheres in this animal, one does not know to what extent these results are applicable to primates, in particular to man. Furthermore, the so-called association areas of the cerebral cortex, which reach their maximal development in man, are poorly developed in the cat and can best be studied in primates. When the differences and similarities between cat and monkey are known, the detailed data available on the cat's cerebro-cerebellar relations may be applied more safely to primates. It is, therefore, highly desirable to study in detail the anatomy of cerebro-cerebellar connections in primates.

---

[1] Present address: Anatomical Institute, University of Oslo, Karl Johans Gate 47, Oslo 1, Norway.

This study deals with one part of the most important pathway mediating impulses from the cerebral cortex to the cerebellum, that is, the corticopontine projection, which is the first link in the corticopontocerebellar pathway (*see* A. Brodal, 1972, for a review). About 19 million fibres are present in the human cerebral peduncle immediately above the pons, while only one million continue into the pyramids. The restiform body, carrying most of the spinocerebellar and olivocerebellar fibres, is said to contain a modest 0·5 million axons on each side in man (Tomasch, 1968).

In the cat, the corticopontine projection exhibits an intricate and precise organization when studied with silver impregnation methods after making small cortical lesions (P. Brodal, 1968*a*, *b*; 1971*a*, *b*; 1972*a*, *b*, *c*; Mizuno, Mochizuki, Matsushima and Sasaki, 1973). The main functional cortical areas project upon different parts of the pontine nuclei. A striking feature is the termination of the fibres in sharply delimited bands or columns and, furthermore, that each minute part of the cortex as a rule projects upon more than one such column. Recently, comparably detailed studies have been performed with the horseradish peroxidase method on parts of the pontocerebellar projection in the cat, disclosing a pattern very similar to that found within the corticopontine projection: restricted cell columns in the pons project on usually more than one part of the cerebellum, and each small cerebellar part receives as a rule from several pontine columns (Hoddevik, 1975; Hoddevik, Brodal, Kawamura and Hashikawa, 1977; Brodal and Walberg, 1977).

Although several authors have studied the monkey's corticopontine projection using silver impregnation techniques, findings in the pontine nuclei are mentioned only briefly, other pathways attracting the main interest (Whitlock and Nauta, 1956; Kuypers, 1960; Kuypers and Lawrence, 1967; Campos-Ortega, Hayhow and Kluver, 1970; Spatz, Tigges and Tigges, 1970; Astruc, 1971). It is not possible from these studies to make out whether the principles of organization are similar to those in the cat. Nyby and Jansen (1951) made a careful study with the Marchi method of the corticopontine projection in the rhesus monkey, finding an overall pattern apparently different from, and less precise than, that in the cat. Doubt exists, however, as to whether these differences are apparent or real, since the Marchi method is less sensitive than the silver impregnation methods and the findings are more difficult to interpret. Furthermore, the lesions used by Nyby and Jansen were much larger than those used in the cat, and often not limited to a particular cortical functional or cytoarchitectonic area. Other Marchi studies in monkeys and studies of human pathological material (*see* Nyby and Jansen, 1951, for references) disagree on important points, and furnish little information with regard to general principles of organization.

The aims of the present study have therefore been to determine which parts of the cortex project on to the pontine nuclei, and whether there are quantitative and qualitative differences between the projections from the various cortical regions; furthermore, to decide whether there is a somatotopical pattern within the projection from the primary sensorimotor cortex, and finally to compare the findings with those made previously in the cat by the present author.

MATERIAL AND METHODS

The brains of 38 adult rhesus monkeys, of which the majority had been used in previous studies (Jones and Powell, 1969, 1970; Kemp and Powell, 1970; Pearson and Powell, 1978), were kindly made available by Dr. T. P. S. Powell. Cortical lesions had been made under pentobarbital anæsthesia, by suction or by removing the pia from the surface of the cortex. After survival periods of three to fourteen days the animals were again anæsthetized and perfused with normal saline, followed by 10 per cent neutral formalin. The brains were removed and stored in fixative for one to three months. Frozen sections were cut at 25 μm in the coronal or transverse plane (fig. 1), and a 1:20 series stained either by the Nauta and Gygax (1954), Fink and Heimer (1967) or Wiitanen (1969) methods. In many instances two of these methods were used on alternate sections from the same brain. The depth and extension of the lesions were checked with the microscope. The sections through the pontine nuclei were drawn, and the terminal degeneration observed in the microscope entered as dots. In the diagrams to follow, representative sections through the pons are shown. The sites of the lesions are described in relation to Brodmann's (1909) cytoarchitectonic map and Woolsey's (1958) physiological map of the sensorimotor cortex.

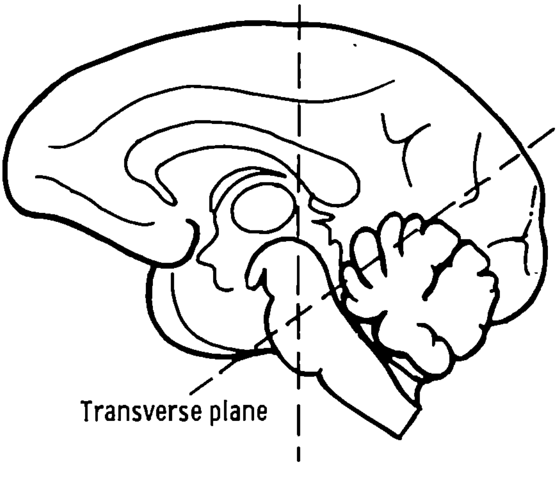


FIG. 1. Diagram showing the planes of sectioning used in the present study. Most series were cut approximately coronally, but the exact plane varies somewhat in different cases.

RESULTS

1. *Degeneration in the Pontine Nuclei after Cortical Lesions*

The distribution and pattern of degeneration in the pontine nuclei is very similar regardless of whether the Nauta and Gygax (1954), the Fink and Heimer (1967) or the Wiitanen (1969) method is used. This is evident from cases where two or more of these methods have been used on alternate sections. In cases with similar lesions but different survival times, no difference can be detected in the distribution of the degeneration. The identification of small amounts of degeneration is rendered difficult in the Nauta and Gygax (1954) sections due to the large number of normal fibres usually impregnated. This makes it possible that in some cases in the present material a small projection may have been overlooked.

In all cases where degeneration of any appreciable amount is found in the pontine nuclei, it is sharply delineated and usually distributed into rostrocaudally orientated slabs or lamella-like areas often only 100–500 μm wide (fig. 2). After large lesions, the degeneration tends to fill the area (*see*, for example, fig. 4) while smaller lesions usually give degeneration in small patches, 50–300 μm in diameter, distributed within the limits of a lamella (*see* figs. 2 and 5).

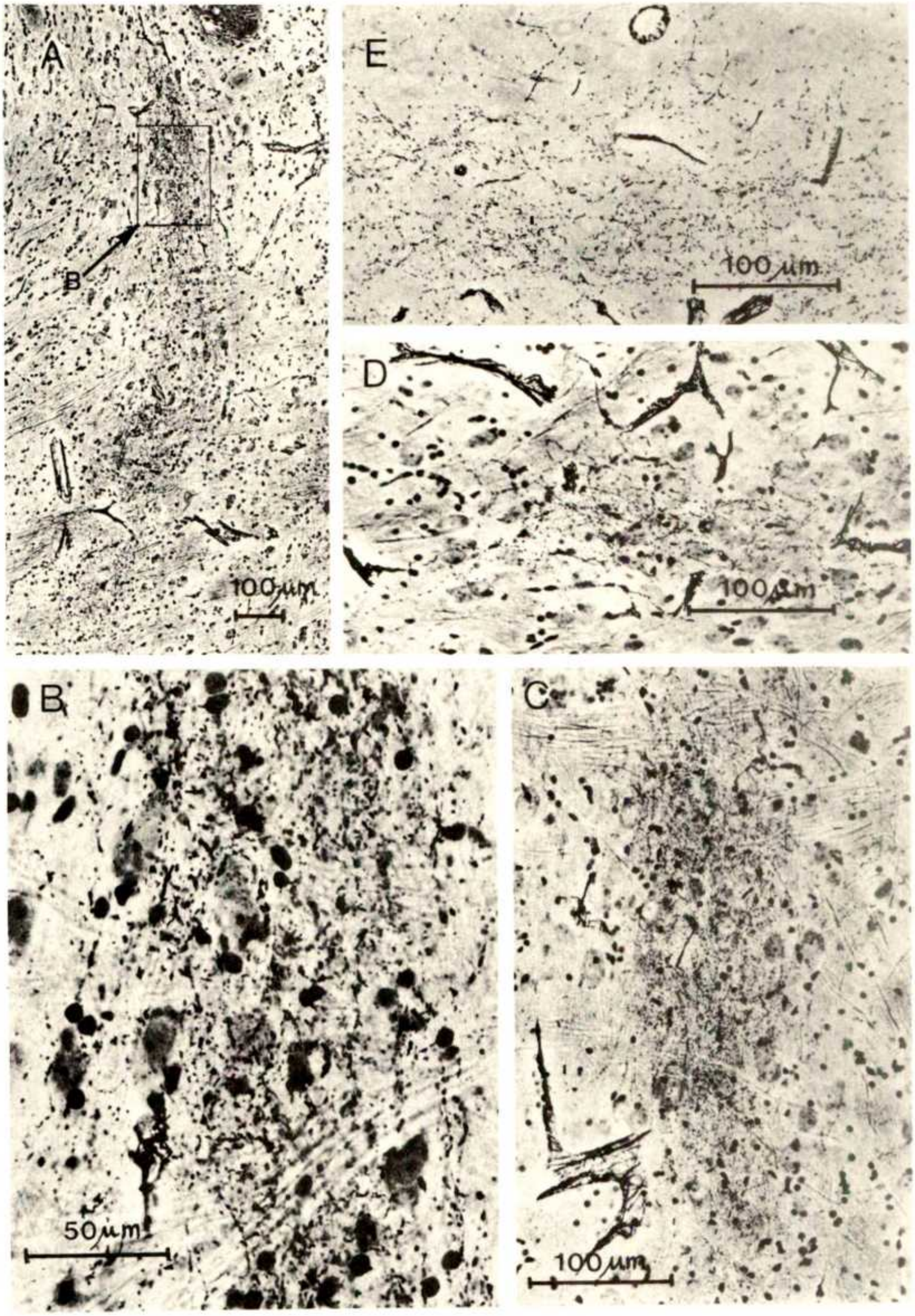
2. *Presentation of Experiments*

Since the main purpose of the present study has been to elucidate the general principles of organization and overall topographical pattern within the corticopontine projection, most of the cases to be presented in the following have lesions aimed at including one cytoarchitectonic or functional area only. A smaller number of cases with lesions restricted to subdivisions of the sensorimotor area will be presented as well, giving information on the question of a somatotopical organization of the corticopontine projection. After large lesions comprising most of the motor cortex, a small amount of contralateral degeneration is found in the pontine nuclei in addition to the massive degeneration occurring ipsilaterally. Smaller lesions of the motor cortex, and large lesions not including the motor cortex gave virtually no contralateral degeneration. Therefore, cases with bilateral lesions were used in several instances. This facilitates the detection of topographical and quantitative differences between projections from the various areas.

The first case shows the pontine distribution of degeneration after a lesion comprising the cortical areas giving origin to most of the pyramidal tract fibres (Kuypers, 1960; Coulter, Ewing and Carter, 1976). In *OM 183* (survival time five days, fig. 3) the *pre- and postcentral gyri* as well as the *superior parietal lobule* are almost completely destroyed, including the cortex in the central and intraparietal sulci. In addition, parts of the inferior parietal lobule are affected. In central and caudal parts the lesion extends considerably into the white matter, and some fibres from areas posterior and medial to the lesion may have been interrupted, but hardly

---

FIG. 2 Photomicrographs showing typical examples of degeneration in the pontine nuclei after small cortical lesions. A, low power photomicrograph of a band-like area of very dense degeneration medial to the peduncle six days after a small lesion of the motor hand area (OM 324, cf. fig. 5, right, section 9). Wiitanen (1969) method. B, from framed area in A. Note the very dense degeneration occurring even after a small lesion, and the sharp transition to normal neuropil. C, example of a very dense patch of degeneration in OM 324 (cf. fig 5, right, section 7) D, a very small patch with moderate degeneration in OM 324 (fig. 5, right, section 13). E, degeneration in the pontine nuclei four days following a lesion of area 5 (OM 241, cf. fig. 8, section 5).


A
B
100 µm
E
100 µm
D
100 µm
B
50 µm
C
100 µm

any from area 6 in front. Thus, the lesion comprises area 4 (motor cortex), areas 3, 1 and 2 (somatosensory cortex) and area 5; with less involvement of area 7.

In the *ipsilateral pontine nuclei* massive degeneration is evenly distributed within almost all parts of the pontine nuclei (fig. 3). However, there are some conspicuous bare areas, more or less surrounding the degenerated regions. The area free from degeneration is very small caudally, but increases in the rostral direction. Sparse degeneration is found in the *contralateral pontine nuclei*, particularly medially in the caudal part.

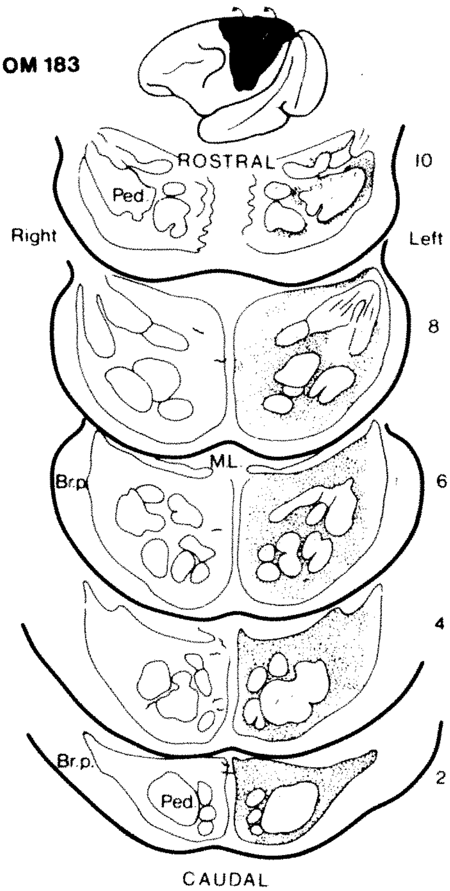


FIG. 3. The distribution of pontine degeneration after a unilateral lesion mainly comprising the sensorimotor cortex and area 5. Area 6 is not involved. The lesion is shown in black in a drawing of the brain (*top*). Below the degeneration is entered as dots in drawings of coronal sections through the pons. Note that the projection is almost entirely ipsilateral, and that the degenerated area is more or less surrounded by a zone free of degeneration. Within the area of termination the fibres are distributed uniformly, in contrast to the patchy appearance following small lesions (*see* figs. 2 and 5). The areas free from degeneration in this case receive fibres from areas 6, 7 and the visual and temporal cortices (*see* figs. 6, 9 and 10). Abbreviations: Br.p. = brachium pontis. M.L. = medial lemniscus. Ped. = continuation through the pons of the cerebral peduncle.

In the following, it will be shown that the areas which are bare in this case (fig. 3) receive afferents from premotor (area 6), visual and temporal cortices, and furthermore, that within the central area of degeneration motor, somatosensory and parietal association areas project differently.

The Sensorimotor Cortex

In OM 58 (survival time twelve days, fig. 4), a large lesion was placed in the *precentral gyrus* (*motor cortex, MI*). The posterior half of area 4 is damaged from the medial margin of the hemisphere to just above the lower end of the central sulcus. White matter is involved over most of the length of the precentral gyrus, but there is no extension into area 3 in the posterior bank of the central sulcus, nor does the lesion extend anteriorly into area 6.

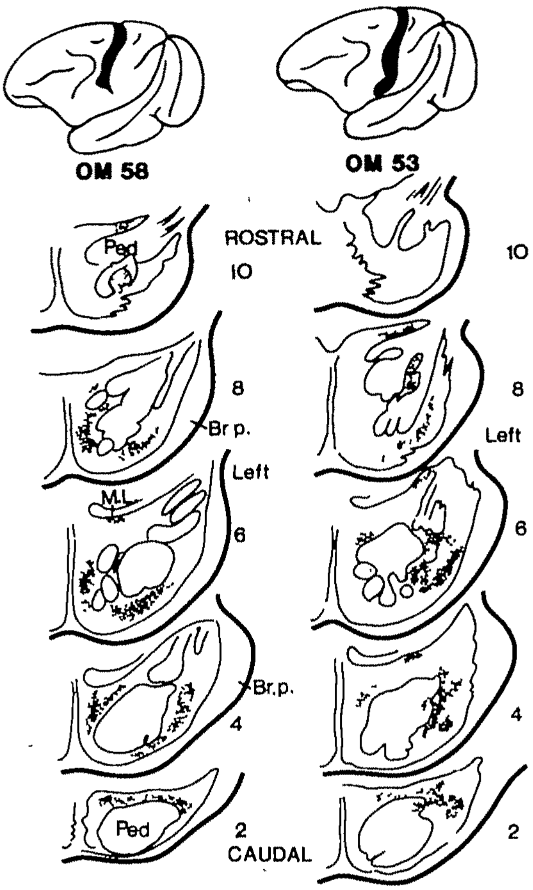


FIG. 4. The pontine projection from the motor cortex (OM 58) and the somatic sensory cortex (OM 53). The pons is cut coronally in both cases but the exact planes are not identical, OM 58 being cut more transversely than OM 53. The motor cortex projects on to two (partly continuous) areas extending rostrocaudally: one medially and one ventrolaterally. The somatic sensory cortex projects mainly on to a rostrocaudal slab laterally, and only to a very small area medially. Note that the somatic sensory cortex projects more laterally than the motor cortex, except caudally, where the overlap appears to be extensive (compare with fig. 5).

In the *ipsilateral pontine nuclei* massive degeneration is found within certain well restricted areas, extending through the length of the pons, but most developed caudally. One area is found medially, and is particularly prominent close to the medial aspect of the ventral part of the peduncle; the other is found ventrolaterally. (The term peduncle is used for the continuation in the pons of the fibres of the crus cerebri). In caudal sections the latter extends far dorsally, while it is restricted to a position ventral to the peduncle at more rostral levels. At some places, particularly caudally, there appears to be continuity between the two areas (fig. 4, section 2). In the *contralateral pontine nuclei*, sparse degeneration occurs within areas corresponding to those showing maximal degeneration on the ipsilateral side.

Corresponding observations are made in another animal with a large lesion restricted to area 4 (*OM 70*, not illustrated). In this case also the rostral part of area 4 is destroyed. The Nauta-Gygax and Fink-Heimer methods were used on alternate sections, giving virtually identical results with regard to distribution of the degeneration.

In *OM 53* (survival time nine days, fig. 4) a large lesion was made of the *left post-central gyrus* (*somatic sensory cortex, SI*). The damage extends from the medial surface to just below and in front of the lower end of the central sulcus. Anteriorly the lesion involves the posterior wall of the central sulcus but the damage to the white matter is slight. Area 4 in the precentral gyrus is not involved.

In the *ipsilateral pontine nuclei* heavy degeneration is found mainly along the lateral aspect of the peduncle. This area of degeneration is found through the rostrocaudal extent of the pons, but predominantly in the caudal two-thirds. At certain levels the slab of degeneration splits into several narrow bands (fig. 4, sections 4–8). There is an additional minor area of degeneration medial to the peduncle (fig. 4, sections 4–6). Only a few isolated degenerated fibres are found in the *contralateral pontine nuclei.*

Some cases with small lesions restricted to anterior or posterior parts of SI indicate that these parts project somewhat differently on to the pons. In *OM 57* and *OM 63* (not illustrated) the small lesions involve areas 2 and 3 in the face and hand regions of SI respectively. There is only very slight involvement of white matter, and fibres from area 4 have most likely not been severed. The distribution of degeneration corresponds to that seen in fig. 4 (OM 53). In *OM 54, 55 and 219*, on the other hand, with lesions restricted to posterior parts of SI (areas 1 and 2) in the trunk and hand regions, virtually no degeneration is found medial to the peduncle.

From what is described above (fig. 4), it appears that the motor and somatic sensory areas project largely to different parts of the pontine nuclei. The motor cortex projects on the whole more medially and ventrally than does the sensory cortex. There appears to be some degree of overlap, particularly caudolaterally.

The *somatotopical patterns* within the projections from SI and MI are most clearly demonstrated in cases with small bilateral lesions, although supportive evidence comes from several cases with small unilateral lesions.

In *OM 323* (survival time six days, fig. 5), small lesions were made of the distal *hand area of the postcentral gyrus* on the right side, of the *leg area* on the *left*. Both lesions extend only very slightly into the underlying white matter and involve mainly areas 1 and 2.

In the *pontine nuclei* dense degeneration is found in small patches within the total projection area of SI, as described above (fig. 4). Except for some patches of low density, however, the degeneration is situated clearly more caudally on the left (leg lesion) than on the right side (fig. 5). Even where degeneration is present on both sides in the same section, the patches are not distributed symmetrically (fig. 5, sections 5–7).

In *OM 324* (survival time six days, fig. 5) small lesions were made of the *MI distal hand area in the precentral gyrus* on the right side, and of the *leg area* on the left. The lesions are restricted to area 4, and only very little white matter is involved.

In the *pontine nuclei* extremely dense degeneration is distributed into sharply delimited bands and patches (figs. 2 and 5) within the total MI projection area as described above (fig. 4). The distribution is clearly different on the two sides. First, the degeneration around the lateral aspect of the peduncle is more caudally located and much more marked on the left than on the right side (fig. 5, sections 3–5). Secondly, around the medial and ventral aspect of the peduncle (sections 5–9) the degeneration is located more medially (and ventrally) on the right than on the left side, the terminal areas taking the form of two curved concentric lamellæ. In addition to these clear differences, more or less isolated patches of degeneration are found on both sides, but as a rule they are not symmetrically situated.

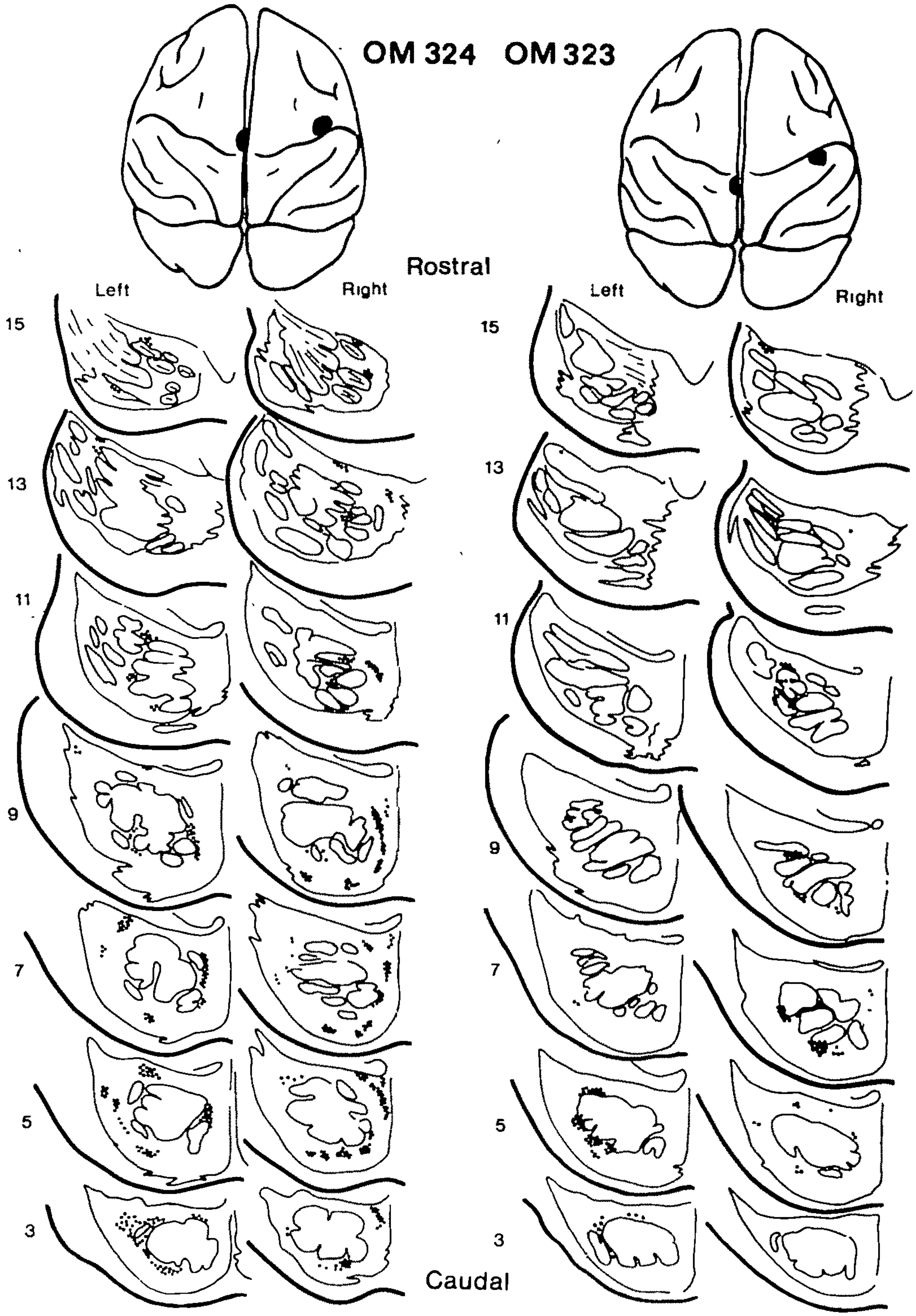
The major differences described above are apparent also when cases with partial lesions of SI (OM 55, 57, 63, 162, 219, 271, not illustrated) and MI (OM 41, fig. 7, and 230, not illustrated) are studied, but due to the patchy distribution of the degeneration over wide areas, more detailed comparison between different cases is extremely difficult.

When comparing the size of the lesions and the amount of degeneration in the pontine nuclei in the cases with small lesions described above, the impression is gained that the projection from the motor cortex is heavier than that from SI. This conclusion, however, concerns only parts of SI on the surface (areas 1 and 2), since isolated lesions of the part of SI in the central sulcus (area 3) have not been obtained.

When comparing the projections from the various subdivisions of the sensorimotor cortex (fig. 5) overlap seems most likely to be present between the projections from SI and MI leg areas. However, even between these the overlap seems only to be partial (fig. 5, sections 3–7) at least in cases with small lesions.

The Frontal Lobe

It appears from the cases to be described that apart from area 4 only area 6 in the frontal lobe gives off a substantial number of fibres to the pontine nuclei. A modest additional projection is found to arise from area 9 (and 8, *see* Discussion).


OM 324
OM 323
Rostral
Left
Right
Left
Right
15
13
11
9
7
5
3
15
13
11
9
7
5
3
Caudal

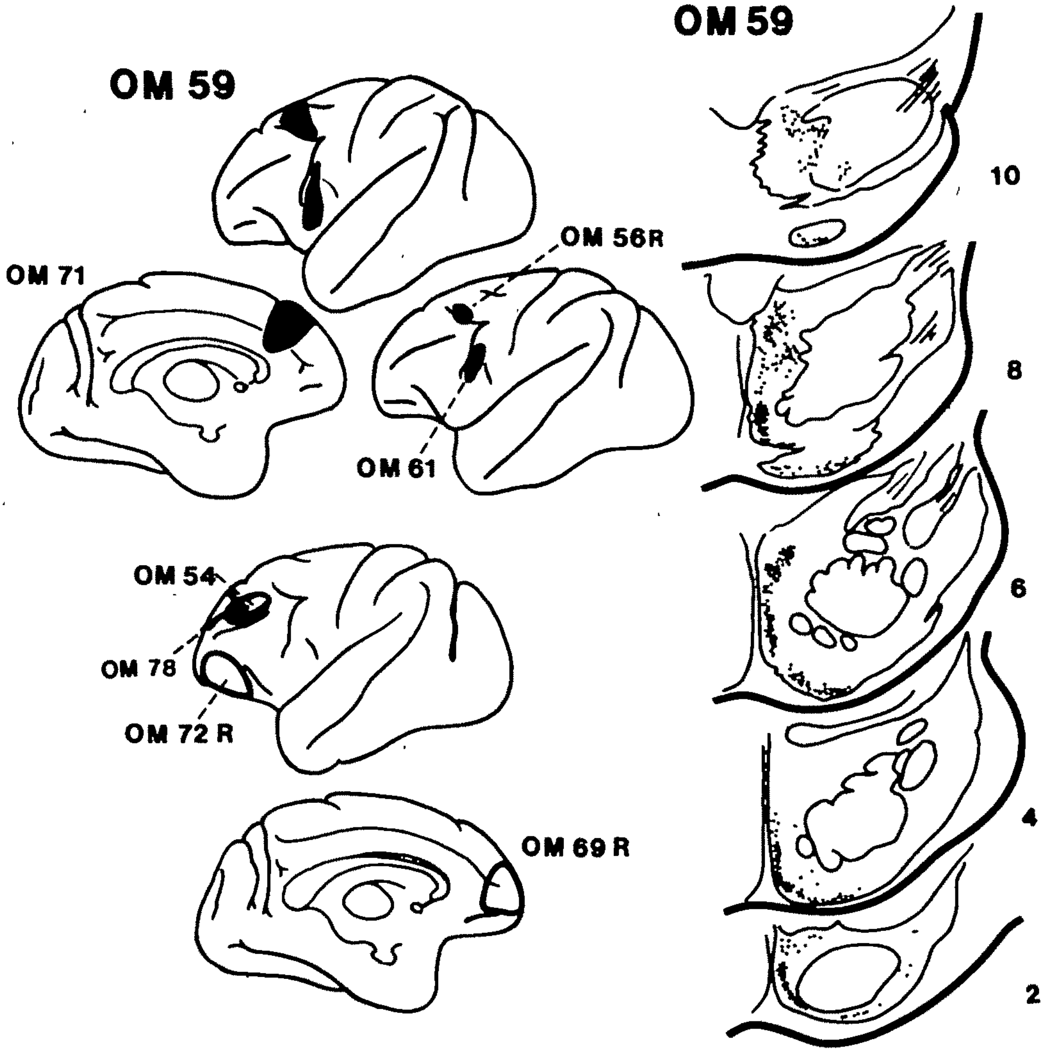


FIG. 6. The pontine projection from large parts of the premotor region (area 6) is illustrated with OM 59. The pons is cut coronally. The degeneration is distributed into a narrow lamella close to the midline and dorsal aspect of the brachium pontis, and extends throughout the rostrocaudal length of the pons. In OM 71 (supplementary motor area), OM 61 (*see* fig. 9) and OM 56 R the distribution of degeneration corresponded to that in OM 59. Below to the left are shown 4 cases with lesions (outline) of prefrontal cortex giving very little pontine degeneration (OM 54, area 9) or none (OM 78, 72R and 69R).

FIG. 5. Two cases with small, bilateral lesions showing the somatotopical pattern within the pontine projection from MI (OM 324) and SI (OM 323) The pons is cut transversely in both cases The drawings of the right halves of the pons have been turned around to facilitate comparisons of the two sides. Note the patchy distribution of very dense degeneration in the pons. The motor leg area (OM 324, *left side*) projects more laterally than the hand area medial to the peduncle (sections 5–9) Ventral and lateral to the peduncle the leg area projects more laterally as well as more dorsally and caudally than the hand area. The pattern within the SI projection is much simpler, with the leg area (OM 323, *left side*) projecting more caudally and a little more dorsally than the hand area. The most marked overlap appears to occur between the two pontine leg areas.

In *OM 59* (survival time thirteen days, fig. 6) the *lesion* involves most of *area 6*. In the *ipsilateral pontine nuclei* moderately heavy degeneration (clearly less than after motor cortex lesions of corresponding size) is confined to a lamella-shaped area close to the midline and ventral aspect of the pontine grey matter. It extends through nearly the whole rostrocaudal extent of the pons. At rostral level, it is found progressively more laterally, covering a larger area but with less heavy degeneration.

In 3 other cases with smaller lesions confined to different parts of area 6, closely similar distributions are found (*OM 56, 61 and 71*, figs. 6 and 9). Whether a lesion is in the medial (OM 71) or lateral part of area 6 (OM 61, fig. 9) appears to make no clear-cut difference with regard to the distribution of the degeneration. However, the plane of sectioning is somewhat different in these cases, making an exact comparison difficult.

In 4 cases with large lesions of *various areas in front of area 6*, little or no degeneration is found (OM 54R, 69R, 72R and 78: survival times eleven, nine, twelve and eight days respectively, fig. 6). In OM 72 a lesion of similar size was placed in the opposite area 5, in OM 69 a smaller lesion in the opposite occipital lobe. Both gave rise to heavy ipsilateral pontine degeneration, while no significant degeneration is found ipsilateral to the frontal lesions (*see* figs. 8 and 9).

In *OM 54* the lesion involves mainly *area 9* above the principal sulcus (fig. 6). The cortex in the sulcus is not involved, neither is area 8. A small number of degenerated fibres, some of them very thin, can be found medially and dorsally in the rostral part of the ipsilateral pons. (A very small lesion was made of the postcentral gyrus of the other hemisphere in this case, giving rise to well delineated terminal fields in the ipsilateral pons).

The Parietal Cortex

OM 41 (survival time eleven days, fig. 7) serves to illustrate the different distribution of the pontine projections from the motor cortex and the parieto-occipital region. There is hardly any overlap in this case.

Lesions restricted to the parts of areas 5 and 7 buried in the intraparietal sulcus have not been obtained. The following therefore concerns the parts of these areas on the surface.

In *OM 241* (survival time four days, fig. 8) large parts of *area 5* on the surface are destroyed, including some of the part on the medial aspect of the hemisphere. There is only slight involvement of the underlying white matter in the middle of the lesion.

In the *ipsilateral pontine nuclei* heavy degeneration is found in a lamella-shaped area extending from dorsomedially to ventrolaterally. Ventrolaterally the lamella is located about half-way between the peduncle and the dorsal aspect of the brachium pontis (fig. 8, sections 3–5). Continuity between the dorsomedial and ventrolateral parts is evident only at some levels. Therefore, what is described here as one lamella may in fact be two largely separate ones. Three other cases with

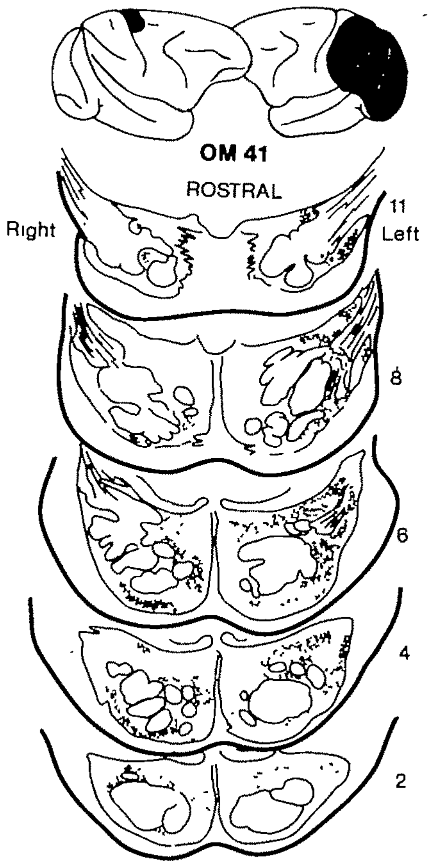


FIG 7. Comparison of the pontine projections from the motor cortex (*right*) and large parts of the parieto-occipital cortex (*left*). The pons is cut at a plane about halfway between transverse and coronal. Note the absence of overlap

lesions restricted to area 5 (*OM 72, 228 and 256*, fig. 8) give closely similar results to those described above. When compared with the distribution of fibres from SI there appears to be a tendency for the fibres from area 5 to terminate external to those from SI (compare figs. 4, 5 and 8). In addition, the impression is gained that area 5 sends relatively more fibres medial to the peduncle than does SI.

There is some evidence that different parts of area 5 project to somewhat different parts of the pontine nuclei. Thus, in *OM 256* (survival time four days, fig. 8) where the lesion does not involve the part of area 5 on the medial aspect of the hemisphere, no degeneration is found caudolaterally (section 2 in fig. 8). In OM 241 (fig. 8) and 72, with lesions involving the most medial part of area 5, marked degeneration is found in this region. As shown above, the cortical motor and somatosensory leg areas project to a pontine region located caudolaterally, apparently very close to the region receiving from the most medial part of area 5.

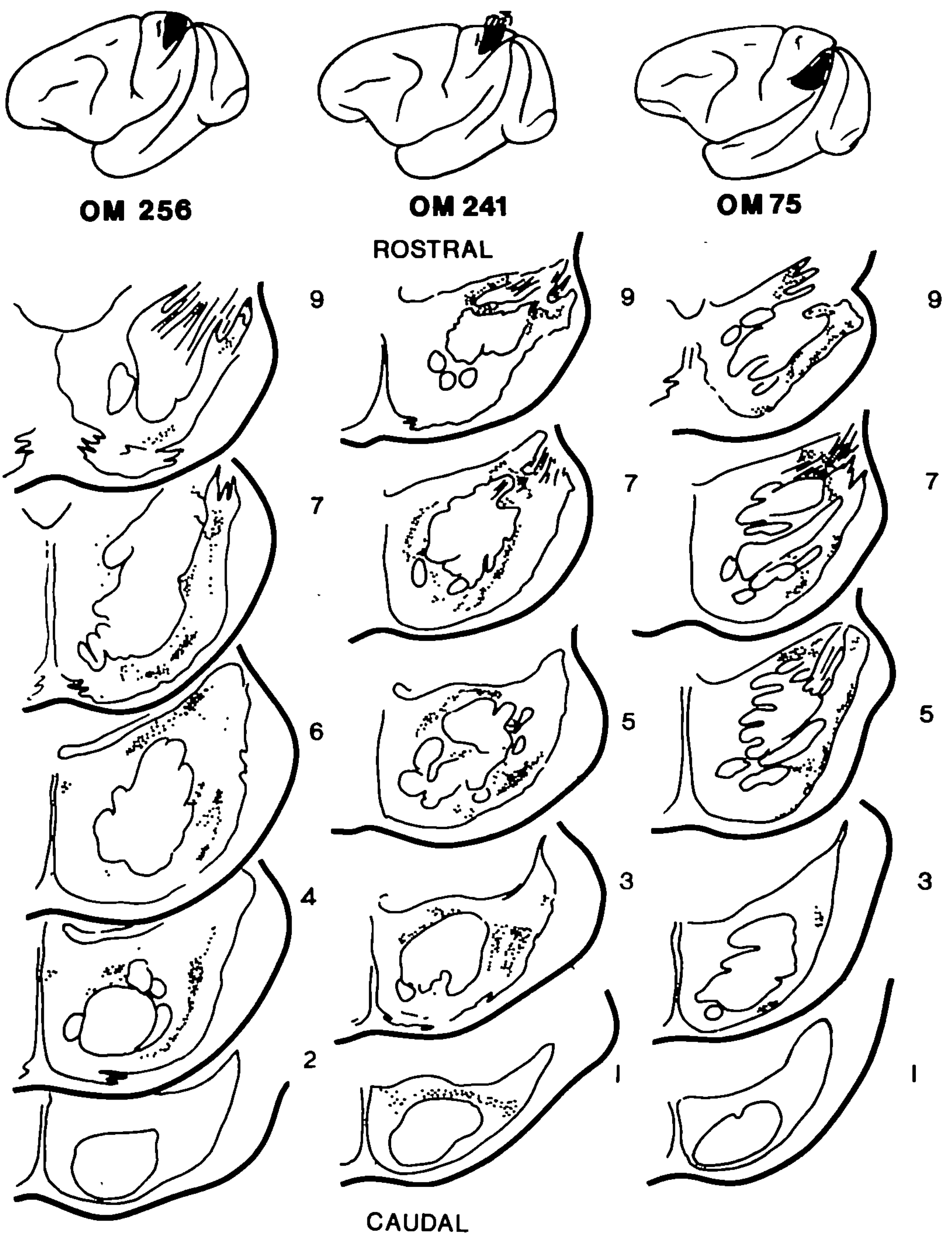


FIG. 8. The pontine projection from areas 5 and 7. The pons is cut coronally in all cases OM 256 and 241 show that area 5 projects to a lamella or column-like area, more or less bending around the lateral aspect of the peduncle (whether in fact the terminal area represents one continuous group or several separate ones has not been decided) Note that only the medialmost part of area 5 (leg representation?) projects laterally in the caudalmost part of the pons, where the sensorimotor leg areas project as well (compare with fig. 5). OM 75 serves to illustrate that area 7 projects to a thin strip or lamella, 'external' to the one projected upon from area 5.

This part of area 5 is in turn connected to the somatosensory leg area (Pearson and Powell, 1978).

In *OM 75* (survival time nine days, fig. 8) a large lesion of *area 7* was made. Although some underlying white matter is involved, fibres from surrounding areas have most likely not been interrupted. In the *ipsilateral pontine nuclei* moderate amounts of degeneration are distributed within a lamella-like area close to the dorsal aspect of the brachium pontis (fig. 8). The lamella appears to bend around the dorsolateral aspect of the peduncle, and extends virtually throughout the rostrocaudal extent of the pons. It is seen from fig. 8 that the degeneration, although altogether making up a lamella-like region, in most sections appears as more or less closely spaced patches.

In 2 other cases with similar, large lesions of area 7 (*OM 257 and 282*, not illustrated) the distribution of degeneration is closely similar to that described above.

When compared with the projection from area 5, two differences are immediately apparent. First, the projection from area 7 is much weaker than that from area 5. It should be stressed that the lesions of area 7 are as large or larger than those of 5, and the Fink–Heimer or Wiitanen methods were used on two or more cases in both groups. Secondly, the lamella projected upon from area 7 is located 'outside' that receiving from area 5, giving a resemblance to the layers of an onion. This is particularly evident ventrolaterally (*see* sections 3–7 in fig. 8) but the impression is gained that it is true also more dorsally, although the degree of overlap may be greater.

Occipital Cortex

Although the material is limited, it gives information on the main points.

In *OM 61* (survival time twelve days, fig. 9) there is a large lesion restricted to parts of *area 17* on the convexity representing the central part of the visual field (Talbot and Marshall, 1941). On the same side a much smaller lesion is placed within area 6 (described above). In the *ipsilateral pontine nuclei* moderate to sparse degeneration is found in a small area dorsolaterally in the rostral part of the pons (marked with a broken circle in fig. 9, sections 6–10). In addition, there is considerably heavier and more extensive degeneration found medially, typical of the area 6 projection (compare with fig. 6). Furthermore, there is heavy degeneration in the superficial layers of the ipsilateral superior colliculus, due to the area 17 lesion. The scarcity of pontine degeneration caused by the area 17 lesion is therefore unlikely to be due to some technical fault.

In *OM 66* (survival time eleven days, fig. 9) there is a large lesion involving parts of *areas 17, 18 and 19* on the convexity, representing central parts of the visual field. In this case very sparse pontine degeneration is found with a lateral distribution similar to that in OM 61 (no degeneration is found medially). In the superficial layers of the ipsilateral superior colliculus there is heavy degeneration.

In *OM 69L* (survival time nine days, fig. 9) the lesion is situated on the medial aspect of the hemisphere, involving mainly Brodmann's *area 19*, but possibly with some minor involvement of area 18. This part of the visual cortex most likely represents peripheral parts of the visual field.

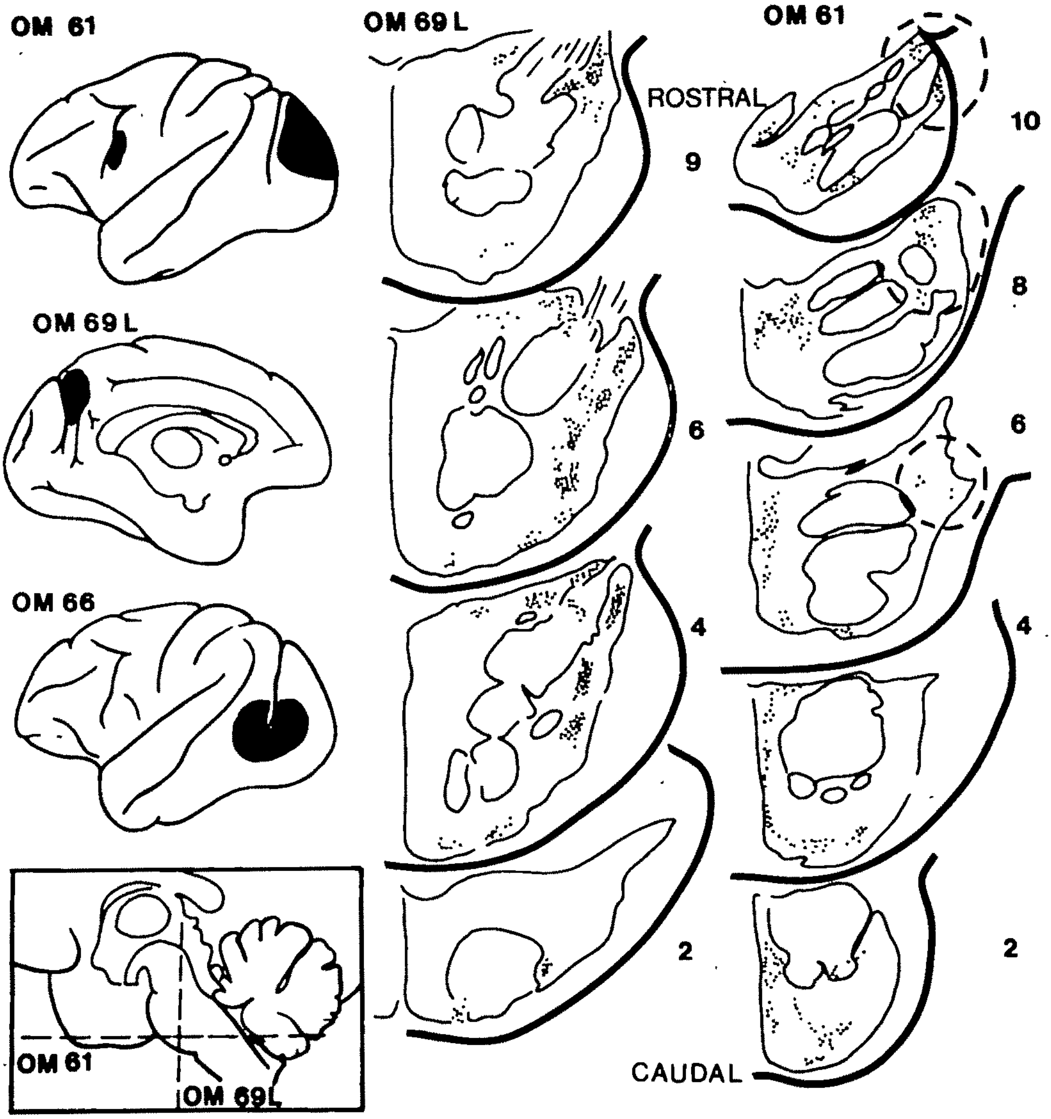


FIG. 9. Three lesions of various parts of the visual cortex are shown to the left. OM 61 illustrates that the parts of area 17 representing the central visual field project sparsely on to a rostrolateral region in the pons (circle with broken line). The small lesion of area 6 in the same hemisphere is responsible for the much more marked degeneration medially (cf. fig. 6). OM 69L shows the distribution of the heavy degeneration occurring after a relatively small lesion of parts of area 19 representing the peripheral visual field (compare with fig. 8). Inset illustrates the different planes of sectioning used in OM 61 and 69.

In the *ipsilateral pontine nuclei* heavy degeneration is found mainly rostrolaterally, extending as a band or lamella in ventral and caudal directions (fig. 9, sections 4–6). The situation of ventral parts of this band is very similar to that seen after lesions of areas 5 and 7, but the degree of overlap between these projections cannot be decided on the basis of this case alone. There is heavy degeneration laterally in the middle rostrocaudal third of the superior colliculus in this case. Corresponding to the smaller lesion, the degeneration in the colliculus is less extensively distributed in OM 69 than in OM 61 and 66.

The above cases show that there is a sparse pontine projection from central parts of areas 17, 18 and 19 terminating rostrolaterally only. Peripheral parts of 19 in addition project heavily on to parts of the pons which apparently also receive from areas 5 and 7.

The Temporal Lobe

The projection from the temporal lobe is found to be scanty, and arising mainly or only in the superior temporal gyrus.

In *OM 56L* (survival time nine days, fig. 10) there is a large lesion involving parts of the *superior and middle temporal gyri* (a much smaller lesion is located in area 6

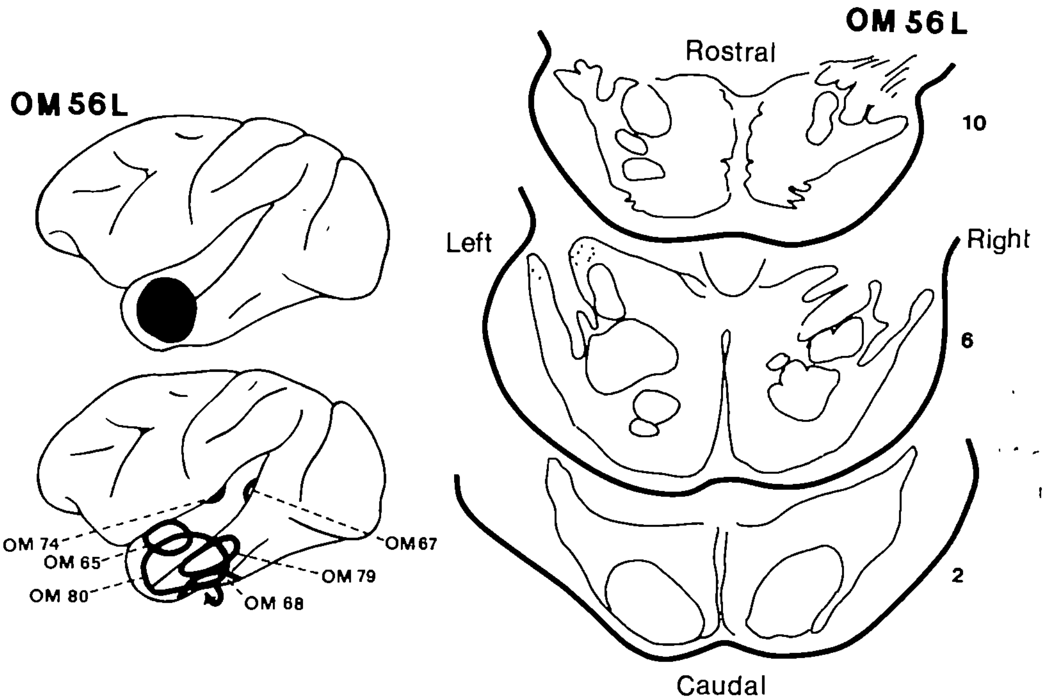


FIG. 10. The termination of corticopontine fibres from the temporal cortex illustrated by OM 56. Only very sparse degeneration is observed somewhat above middle rostrocaudal levels in the dorsolateral part of the pons (coronal sections). Below to the left are illustrated lesions (outlined) giving very sparse or no degeneration in the same region.

of the other hemisphere, fig. 6). In the *ipsilateral pontine nuclei* a small locus of degeneration is found dorsolaterally somewhat above the middle half of the pons. (In the pontine nuclei on the other side, much more degeneration is found with a typical area 6 distribution).

In *OM 67* (fig. 10) with a small lesion of the caudal part of the superior temporal gyrus, a small locus of moderate degeneration is found in one section only, dorsolaterally, somewhat below the middle half of the pons. Even less degeneration in the same region is found in *OM 74* (fig. 10) with a very small lesion of the superior bank of the superior temporal gyrus (probably involving the auditory cortex). In 4 other cases with large lesions of various parts of the temporal lobe, no significant degeneration was found in the pontine nuclei (OM 65, 68, 79 and 80, fig. 10).

Cingular Gyrus

Only one brain is available with a lesion restricted to the cingular gyrus. In *OM 60* (survival time thirteen days, not illustrated) large parts of the cingular gyrus overlying the rostral two-thirds of the corpus callosum have been damaged. Only a few degenerated fibres are found scattered in the ventrolateral part of the *ipsilateral pontine nuclei* in or close to the region receiving from the motor cortex. Thus, this experiment indicates that the anterior two-thirds or so of the cingular gyrus sends only a very few fibres to the pontine nuclei.

DISCUSSION

This study presents evidence of a precise and intricate pattern of organization within the corticopontine projection of the monkey. Furthermore, the relative quantities of projections from the main cortical regions have been elucidated. Before discussing these results in some detail, a few comments on their validity are appropriate.

When it is said that certain cortical regions project to different parts of the pontine nuclei, this is always based on similar findings having been made in several experiments. Furthermore, the use of bilateral lesions strengthens the conclusions concerning topographical differences (*see*, for example, figs. 5 and 7). In the corticopontine (P. Brodal, 1968*a*, *b*; 1971*b*; 1972*a*, *b*, *c*) and pontocerebellar projections of the cat (Brodal and Walberg, 1977) certain differences were disclosed only after use of bilateral lesions or injections, which served to minimize problems such as individual variations, differences in planes of sectioning, and differences in quality of staining.

With regard to quantitative differences, only very large ones have been regarded as significant, and the conclusions drawn concern *relative* quantities more than the question of a projection versus no projection from an area. Only cases with similar sized lesions, or with the largest lesion in the sparsely projecting area, were used for this purpose. In several cases one lesion was placed in each hemisphere; one in a region giving off many fibres, the other in a sparsely projecting part. This largely eliminates random variations due to differences in survival time, stainability of fibres or other technical differences which may occur in different brains. In addition, with lesions of the visual cortex, the intensity of degeneration in the superior colliculus served as a useful check of the effective size of the lesion and the technical standard of the sections. However, special problems in interpretation may arise when the projection fibres are very thin, as are those from the prefrontal cortex. Even if the survival times used here should be sufficient for degeneration of thin fibres (De Vito and Smith, 1964; Kuypers and Lawrence, 1967), the recognition of their terminal fields may be difficult; nevertheless it seems unlikely that any major amount of terminal degeneration has been missed.

Origin of Corticopontine Fibres

The cortical regions giving origin to the densest and most extensive pontine projections are found to be areas 4, 3, 1, 2 and 5, and in addition, certain parts of the visual cortex (fig. 11B). This is largely in agreement with Nyby and Jansen's (1951) findings with the Marchi method in the rhesus monkey. Although not explicitly stated, the same main areas of origin appear to have been found by Kuypers and Lawrence (1967) in their study with silver impregnation methods. With the exception of the visual cortex, these same areas (4, 3, 1, 2 and 5) give origin to the majority of corticospinal fibres in the monkey (Kuypers, 1960; Russel and De Myer, 1961; Coulter, Ewing and Carter, 1976) and are also the main areas of origin of corticostriatal fibres (Kemp and Powell, 1970).

A somewhat less heavy contribution to the corticopontine projection comes from the areas in front of and behind this central region; that is, from areas 6 and 7. Of these two areas, probably area 6 contributes most. When moving further into frontal and temporal association areas, as well as the cingular gyrus, progressively fewer fibres appear to be sent to the pontine nuclei.

Only a case with a lesion of the anterior two-thirds of the cingular gyrus was studied. In the cat there is evidence for a pontine projection from its posterior part (Brodal, 1972*b*). Müller-Preuss and Jürgens (1976) found autoradiographically a pontine projection from the vocalization area in the anterior part of the cingular gyrus of squirrel monkeys. Nothing is said about the quantity of projection and the distribution appears very similar to that found here after area 6 lesions. Some involvement of area 6 may therefore theoretically account for their findings; another possibility is of course that the greater sensitivity of the autoradiographic method reveals a projection too small to be found by the Nauta method.

Powell (1973, p. 273) stated on the basis of anatomical studies of cortico-cortical connections that 'When connections cease going into areas 4 and 6 from both frontal and from parietotemporal lobes they begin to go into limbic regions', the latter being related to visceral and emotional spheres more than somatic. The cerebellum is obviously concerned mainly with somatic functions, and the origin of the bulk of corticopontine fibres is in keeping with the role of the cerebro-cerebellar relations in motor control. The motor and somatosensory regions need no further comment in this respect. Area 6 has a major outflow to area 4 and is certainly of importance in movement control, although its role is not yet worked out in detail. Whether area 6 has a spinal projection has been a matter of dispute (cf. Russel and De Myer, 1961; Kuypers, 1960; Wiesendanger, Séguin and Künzle, 1974). However, Jones and Wise (1977) found labelled cells in area 6 of the monkey after horseradish peroxidase injections in the spinal cord. Area 5 contains many cells apparently functioning in command roles with regard to certain movements, such as when a monkey '. . . projects his arm or manipulates with his hand within the immediate extrapersonal space to obtain an object he desires. . . .' (Mountcastle, Lynch, Georgopoulos, Sakata and Acuna, 1975, p. 905; *see also* Lynch, Mountcastle, Talbot and Yin, 1977). Since these cells are active in advance of the movement, it is conceivably of importance that the cerebellum gets a 'copy' of their messages in order to contribute to, for example, the smoothness of the movement (*see* Ito, 1970; Allen and Tsukahara, 1974). However, it should be emphasized that other types of cells are found in areas 5 and 7 as well (Mountcastle *et al.* 1975; Lynch *et al.* 1977) and one does not know the properties of the cells projecting to the pons from areas 5 and 7.

Recently, some interesting data have been presented with regard to the origin of corticopontine fibres from the sensorimotor cortex. Jones and Wise (1977) injected small amounts of horseradish peroxidase in parts of the pontine nuclei in monkeys and found labelled cells of medium to large size in middle parts of lamina V in areas 4, 3, 1 and 2. Furthermore, after a single pontine injection, labelled cells in the cortex tended to be distributed in several narrow (0·5–1 mm) bands extending mediolaterally. Their relation to the pontine patches and lamellae-like regions of terminal degeneration remains to be elucidated; a simple arrangement of one cortical band projecting to one pontine lamella seems unlikely in view of the large number of cortical bands labelled even after a very restricted pontine injection.

The present conclusion that few corticopontine fibres emanate from *areas in front of area 6* needs some comment. First, no case with a lesion involving area 8 was available. However, Astruc (1971) and Kuypers and Lawrence (1967) found a pontine projection which was said to be 'light and scattered' (Astruc, 1971) from area 8 in rhesus monkey with the Nauta method. Künzle and Akert (1977) after injections of radioactively-labelled proline in area 8 found 'moderate to dense grain accumulations' in the pontine nuclei, but at present it is hard to compare these findings in quantitative terms with those obtained by degeneration methods. The present finding of a sparse corticopontine projection from areas in front of area 8 ('prefrontal cortex'), arising mainly in area 9, seems to agree with previous studies in monkey using degeneration methods (*see* Nyby and Jansen, 1951 for references to the older literature). Kuypers and Lawrence (1967) found 'only a limited number of fibres to the brain-stem' after lesions comprising presumably areas 9 and 10, and the fibres were said to be fewer than after lesions of area 8. A pontine projection from area 9 was described in another degeneration study (De Vito and Smith, 1964) and also mentioned in an autoradiographic investigation

(Goldman and Nauta, 1976) but nothing was said with regard to quantity. In a careful study of a large number of leucotomized human brains, Beck (1950) found definite gliosis and cell shrinkage in restricted parts of the pontine nuclei in cases with lesions limited to prefrontal areas. However, no changes were found when lesions were restricted to the frontal pole and the orbital cortex, in agreement with the present findings. It seems therefore justified to conclude on the basis of the present and previous studies in primates that area 8 probably has a more modest pontine projection than area 6, and that even fewer fibres emanate from area 9. There is no good evidence for projections from other prefrontal areas.

In the cat there is a modest projection from the orbital gyrus (probably corresponding to parts of the orbital cortex in primates) to areas in the pons partly coinciding with those receiving from SI and SII (*see* Brodal, 1971*b*).

The origin of corticopontine fibres from the *occipital lobe* (*visual cortex*) has been a matter of dispute (*see* Nyby and Jansen, 1951; P. Brodal, 1972*a*, *b*). In the cat, parts of area 17, 18 and 19 representing peripheral parts of the visual field have strong pontine projections, while central parts (most conclusively shown for area 17) project sparsely (P. Brodal, 1972*a*, *b*). This has recently been shown also by physiological methods (Albus and Donate-Oliver, 1977). The present material alone can only give partial answers to which parts of the monkey visual cortex project to the pons, but taken together with previous results, certain disagreements in the literature seem to be more apparent than real. Thus, several authors finding only a modest pontine projection from the visual cortex in the monkey (Mettler, 1935; Sunderland, 1940; Kuypers and Lawrence, 1967; Spatz *et al.* 1970) had lesions restricted to the cortex on the convexity representing the central 4–10° of the visual field (Talbot and Marshall, 1941). Nyby and Jansen (1951) found heavy pontine degeneration only after a lesion involving parts of areas 17 and 18 situated on the medial wall of the hemisphere, representing peripheral parts of the visual field. The present study gives evidence of a heavy projection from parts of area 19 on the medial wall as well (fig. 9). Two lesions on the convexity, involving parts of areas 17, 18 and 19 gave modest and more restricted degeneration (fig. 9). Taken together, this makes it fairly certain that peripheral parts of areas 18 and 19 have a heavy pontine projection while central parts of 17, 18 and 19 project sparsely. It remains to be decided whether peripheral parts of area 17 in the monkey send more fibres than central parts, as is the case in the cat. Nevertheless, at the present stage there is reason to assume that, with regard to origin, occipitopontine projections are principally similar in monkey and cat.

The pontine projection from the *temporal lobe* is found here to be sparse and to arise primarily from the superior temporal gyrus. This is in agreement with the conclusions of Nyby and Jansen (1951) using the Marchi method, and Whitlock and Nauta (1956) with the Nauta method. On the basis of human pathological material several authors have concluded that the massive temporopeduncular bundle of Türck terminates in the pontine nuclei (*see* Nyby and Jansen (1951) for references). However, Whitlock and Nauta (1956) state that in the monkey '... the bulk of Türck's temporopeduncular bundle appeared to distribute diffusely dorsalward to lateral tegmental areas rather than to the pons'. It would seem likely that this is the case also in man.

In the cat, the modest projection from the temporal lobe homologue arises mainly in the second auditory area (A II) with a smaller contribution from A I (P. Brodal, 1972*c*). Whether this is the case also in primates cannot be answered from the present or previous studies, due to the technical difficulties involved in damaging large enough parts of the auditory cortex in isolation. Typically, the single lesion of the present material involving the auditory cortex was too small to allow conclusions with regard to quantity of projection (OM 74, fig. 10).

Termination of Corticopontine Fibres

It is a striking feature of the monkey's corticopontine projection that the fibres terminate within sharply circumscribed regions, taking the form of rostrocaudally orientated slabs or lamellæ.

In the cat, the correspondingly arranged pontine terminal areas have been termed columns (P. Brodal, 1968*a*, *b*). Obviously, the complexity of the terminal regions makes an accurate description difficult. The terms chosen are therefore to some degree arbitrary and can only give a crude impression of the actual three-dimensional shape of the terminal areas. In order to avoid associations with the concept of columns as used in the cerebral cortex, this term has not been used here.

The sharp localization of the degeneration was first observed by Nyby and Jansen (1951) in the monkey and subsequently the pattern was worked out in more detail in the cat by the present author. Furthermore, in the monkey as well as in the cat, each cortical area often projects on to apparently separate pontine cell groups. When observed in a single section, the degeneration is usually found in several small patches. In order to decide whether these are continuous with similar patches in the adjoining sections, the plane of sectioning is critical, and different planes have to be employed systematically. This has been done to a large extent in the cat showing that the terminal areas as a rule constitute continuous regions (*see* Brodal, 1968*a*, 1972*a*). However, this seems to be so only when the lesions are large, comprising, for example, most of the motor or sensory cortex (*see* figs. 3 and 4). Following small lesions, the degeneration regularly occurs as numerous small patches or fragments of a lamella (*see* figs. 2 and 5). In some cases with small differently placed bilateral lesions of the sensorimotor cortex, patches on the two sides are often found to be situated almost, but not quite, symmetrically (as judged from superimposing the findings from one side on to the other). Interestingly, a somewhat similar pattern of divergence has been described in the cerebellar corticonuclear connections (Brodal and Courville, 1973; Courville, Diakiw and Brodal, 1973) and the projection from the ventrolateral thalamic nucleus (VL) to the motor cortex (Asanuma, Fernandez, Scheibel and Scheibel, 1974; Rispal-Padel and Grangetto, 1977; Strick, 1976).

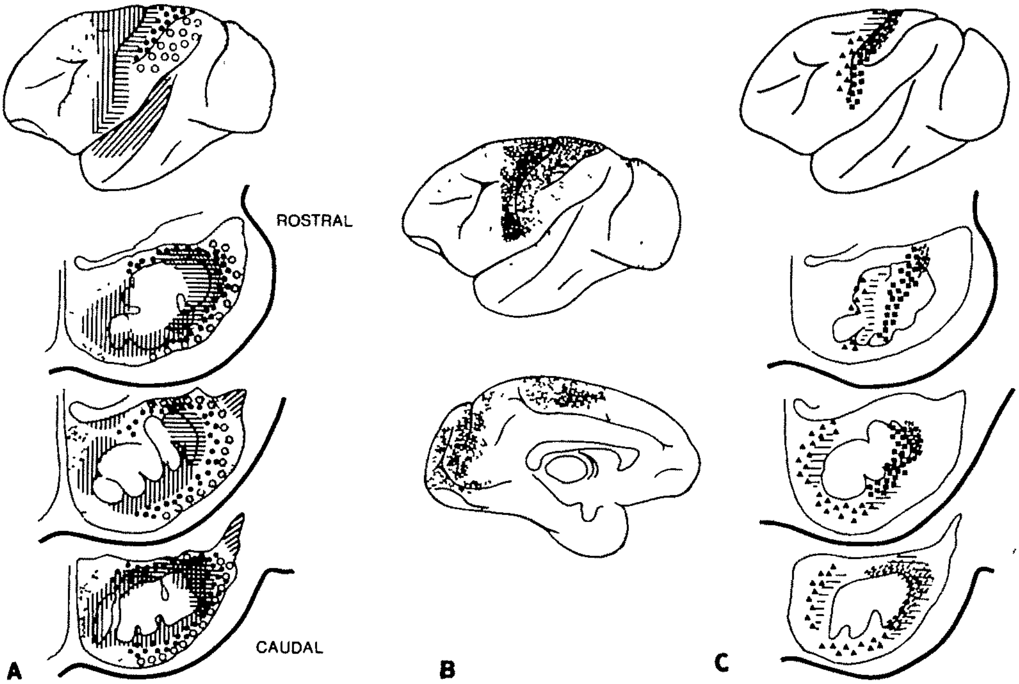


FIG 11 Schematic summary of the main findings of the present study. A, termination of corticopontine fibres from various cortical regions as appearing in three transverse sections. Note the tendency for termination in concentric lamellæ. B, approximate relative density of corticopontine fibres arising in various regions of the cortex. C, a simplified representation of the somatotopical pattern within the pontine projections from the motor cortex (triangles and horizontal lines) and the sensory cortex (squares and oblique lines).

Although the present material allows no final conclusions as to the ultimate precision of the corticopontine projection, certain topographical differences are very clearcut. Before discussing these, it should be emphasized that the sites of termination of fibres from various regions as found here agree on the whole with the findings of Nyby and Jansen (1951), and with less systematic observations in other primate studies (Whitlock and Nauta, 1956; Kuypers, 1958, 1960; De Vito and Smith, 1964; Kuypers and Lawrence, 1967; Campos-Ortega *et al.* 1970; Spatz *et al.* 1970). The present study, however, provides a more detailed and comprehensive scheme than previously available.

The overall arrangement of terminal fields of fibres from various cortical regions resembles to some degree the layers of an onion; fibres from the sensorimotor region terminate in a central core while fibres from surrounding areas are added externally (fig. 11A). Area 6 projects to the medial and ventral part of an external 'layer' while areas 5 and 7 project to its lateral and dorsal parts. The visual cortex projects to a 'layer' further laterally (fig. 11A).

Area 9 projects dorsally in rostromedial parts of the pontine nuclei (De Vito and Smith, 1964; present study), probably overlapping the area 6 projection. Area 8 appears from degeneration studies to project on to virtually the same region as area 9 (Kuypers and Lawrence, 1967; Astruc, 1971). However, Künzle and Akert (1977) after tritium-labelled proline injections of area 8 in monkey found rather widespread labelling in the pontine nuclei, notably in the dorsolateral nucleus. Since the superior colliculus receives a projection from area 8, and projects on to the dorsolateral pontine nucleus (Kawamura and Brodal, 1973; and others), the labelling in the dorsolateral nucleus described by Künzle and Akert may possibly be due to transynaptic transport which is known to occur in the visual pathways to the pons (*see* Casagrande and Harting, 1975). Further study is needed to clarify this point.

From a functional point of view the important question is to what degree impulses from different cortical areas converge on to single pontine cells. The overall arrangement as outlined above indicates that each cortical area or region projects to an at least partly separate part of the pontine nuclei. Fig. 7 gives a striking example of the difference between the projection from the motor cortex and large parts of the parieto-occipital cortex, as revealed by bilateral lesions; there is hardly any overlap at all in this case. Areas 4 and 6 are further examples of cortical areas projecting to adjacent regions apparently with very little overlap (compare figs. 4 and 6, *see also* fig. 11A). Only limited overlap is found between projection areas of MI and SI (fig. 4), and most of the overlap appears to concern the representation of the leg (fig. 5). Since the most skilled and diversified movements are carried out by the upper extremities, it seems conceivable that the cerebellum needs more precise information from areas related to these than from those related to the lower extremities. Although it appears likely that a larger part of the pontine nuclei is related to the cortical hand-area than to the foot-area (*see* fig. 5), the material is not suited to answer this question decisively. Interestingly, there is a much clearer separation between pontine 'motor' and 'sensory' projection areas in the monkey than in the cat (fig. 12). This may reflect the clearer functional separation between motor and somatosensory cortices in the monkey than in the cat. There is suggestive evidence of further differences between subdivisions of SI with regard to pontine projections, in so far as only lesions involving anterior parts of SI (area 3) gave rise to significant degeneration medial to the peduncle. This difference is unlikely to be due to inadvertent damage of area 4 since the degeneration medially is located somewhat differently after area 4 lesions. A similar difference is reported by Jones and Wise (1977) using selective injections of tritiated amino acids in cytoarchitectonic subdivisions of SI. Coulter and Jones (1977) reported somewhat different sites of termination in the spinal cord dorsal horn of fibres from areas 3, 1 and 2 respectively.

Although there may be extensive overlap between the projections from SI and area 5, certain cells would be expected to be influenced only from one or other area since area 5 projects at least partly 'external' to SI (figs. 4, 8 and 11A). The same considerations apply to the projections from areas 5 and 7 where overlap would be expected to occur mainly dorsally (figs. 8 and 11A). Also in the cat areas 5 and 7 appear to project to partly different regions in the pontine nuclei (Mizuno *et al.* 1973).

There is probably extensive overlap between the pontine projections from areas 5 and 7 on the one hand, and the visual cortex on the other, but this seems to concern particularly the projection from area 19 since area 17 projects only to a restricted region laterally (compare figs. 8 and 9). Also in the cat, area 17 (and 18) project to more restricted parts of the pontine nuclei than area 19, the latter overlapping with areas 5 and 7 (P. Brodal, 1972*b*). Parts of area 17 (and probably area 18) representing different parts of the visual field project differently in the cat (P. Brodal, 1972*a*, *b*); whether a corresponding localization exists in the monkey cannot be decided from the present material.

The patchy character and irregular course of the pontine terminal areas make exact comparison between different cases extremely difficult. Thus, when it was said above that projections from cortical regions overlap in the pons, this may be less than is apparent. Although further anatomical studies with small bilateral lesions or combination of degeneration and autoradiographic techniques may help to clarify such points, physiological studies are needed to determine the degree of convergence at the cellular level. So far this has been done only in the cat (Oka, Sasaki, Matsuda, Yasuda and Mizuno, 1975; Rüegg and Wiesendanger, 1975; Baker, Gibson, Glickstein and Stein, 1976), and lack of documentation of the exact location of the cells investigated sometimes hampers a correlation with the anatomical data. On the whole, however, the physiological findings point to only a limited convergence from different cortical areas on to single pontine cells, in agreement with the anatomical data in cat and monkey.

On the other hand some electrophysiological studies may give the impression of a diffuse pattern within the cerebrocerebellar pathways since stimulation of one part of the cerebral cortex tends to give evoked potentials in wide parts of the cerebellum (Dow, 1942; Snider and Eldred, 1952; Sasaki, Oka, Kawaguchi, Jinnai and Yasuda, 1977). However, the rather precise and complicated organization of the corticopontine projection in cat and monkey, and of the pontocerebellar projection in the cat (Hoddevik, 1975; Hoddevik *et al.* 1977; Brodal and Walberg, 1977) appears not readily compatible with a diffuse spread of connections to various parts of the cerebellum. It seems more likely that although the extensive convergence and divergence within the corticopontine and pontocerebellar projections make possible transmission from one part of the cerebral cortex to wide areas in the cerebellum, the projections would not be diffusely distributed but rather focused on numerous discrete areas. This seems also more compatible with the relatively specific properties of pontine cells mentioned above and of Purkinje cells (presumably influenced from the cortex) when tested in relation to active movements (Harvey, Porter and Rawson, 1977). Another factor which may contribute to the impression of diffuseness of cerebrocerebellar interconnections is that, although quantitatively most important, the pontine nuclei are not the only relays for impulses travelling from the cerebral cortex to the cerebellum. In addition, the lateral reticular nucleus, the paramedian reticular nucleus and the nucleus reticularis tegmenti pontis all receive relatively diffuse projections from the cerebral cortex and send mossy fibres to various parts of the cerebellum (*see* A. Brodal, 1972; Allen and Tsukahara, 1974).

Somatotopical Patterns within the Monkey Corticopontine Projection

By use of small, bilateral lesions, a clear somatotopical pattern was demonstrated in the pontine projections from MI and SI (*see* figs. 5 and 11c). In fig. 11c the main features are summarized diagrammatically. The pattern within the projection from SI seems relatively simple, with the leg represented mainly more caudally (and dorsally) in the pons than the arm. A very similar organization has been described in the cat (P. Brodal, 1968*a*) and rat (Wise and Jones, 1977).

The somatotopical pattern within the motor cortex projection is more complicated than that within the SI projection. Medially, the fibres from the MI leg area terminate in a lamella mainly lateral to the one projected upon from the hand area. Laterally, the leg is mainly represented more laterally and dorsally than the hand, but as with SI the strongest leg projection is found far caudally, in fact extending further caudally than the SI leg projection (*see* fig. 5). Except for minor differences this somatotopical pattern is very similar to that in the cat (P. Brodal, 1968*a*), although the separation of termination into two distinct pontine areas is less clear in the monkey than in the cat.

There is some evidence from the present material of a somatotopical pattern within the pontine projection from area 5 (fig. 8) similar to that within the projection from SI. This would fit the observation of Sasaki *et al.* (1977) that stimulation of medial parts of area 5 tends to evoke potentials in rostral parts of the anterior lobe (leg representation) while more caudal parts are activated from lateral parts of area 5.

There is suggestive evidence that after small lesions, in some places in the pons where the projections from cortical hand and leg areas terminate close together in patches, they do not actually overlap (*see* fig. 5). This bears some resemblance to the mosaic-like input to some Purkinje cells as described by Eccles and co-workers (Eccles, Sabah, Schmidt and Táboříková, 1972). Thus, closely adjacent Purkinje cells were often found to have widely different peripheral inputs (for example, arm versus leg).

Comparison of Corticopontine Projection in Cat and Monkey

As has been discussed above, the general principles of organization are very similar in the corticopontine projections of cats and monkeys, for example, termination within slabs or lamellæ and the somatotopical patterns. Certain differences are evident, however, when comparing the main sites of termination of fibres from certain cortical regions as emerging from the present study and from previous studies in the cat (P. Brodal, 1968*a*, 1972*a*, *b*; Mizuno *et al.* 1973). This concerns least the sensorimotor cortex which in both animals projects largely to a central region around the peduncle. Fig. 12 gives a schematic representation of the main points of difference. When comparing projections from area 6 (P. Brodal, unpublished observations in the cat), the parietal association areas (5 and 7), and the visual cortex in the two species, the differences are very marked. On the whole,

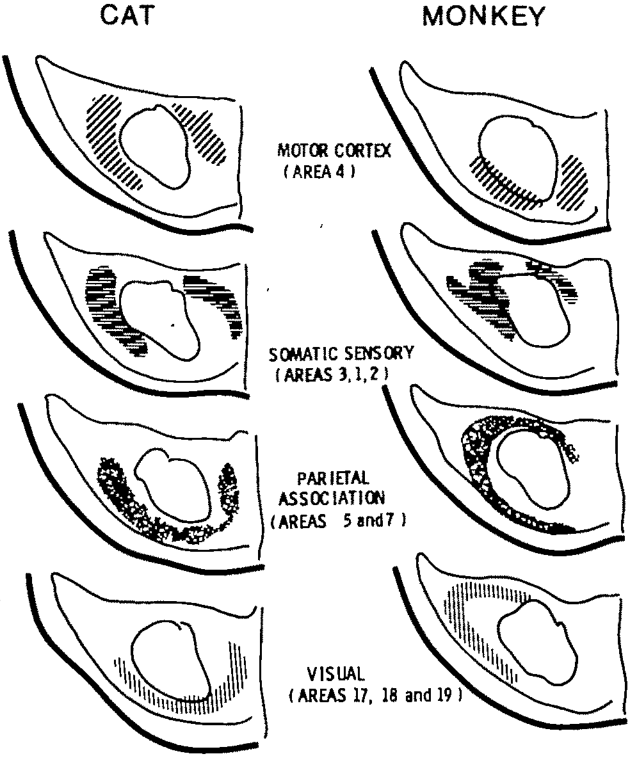


FIG. 12. Schematic representation of some of the main differences between cat and monkey corticopontine projections, based on the present study and previous findings in the cat (P. Brodal, 1968*a*, 1972*a*, *b*; Mizuno *et al.* 1973). The projections from all cortical regions are shown as terminating in a transverse section at the same rostrocaudal level

in the cat these areas project medially as well as laterally, while in the monkey area 6 projects only medially, and areas 5 and 7 and the visual cortex project only laterally. These differences make it difficult to correlate the corticopontine projection areas in monkey with data on the pontocerebellar projection in the cat in order to determine the part of the cerebellum connected to a particular part of the cerebral cortex. Although lack of knowledge of the organization of the monkey's pontocerebellar projection makes it difficult to decide, on anatomical evidence, whether the differences between the corticopontine projections in cat and monkey reflect differences in cerebrocerebellar organization, physiological studies indicate that there are indeed such differences (*see* Sasaki *et al.* 1977). Thus, premotor and parietal association areas show clear differences in their pontine projections in cat and monkey, and when stimulated they give evoked potentials in somewhat different parts of the cerebellum in the two species. There are also certain topographical differences between cerebello-cerebral connections in cat and monkey (Sasaki, Kawaguchi, Oka, Sakai and Mizuno, 1976). Such differences in connectivity may mean that the tasks of certain parts of the cerebellum are not identical in cat and monkey, or, alternatively, that different groups of neurons are used to accomplish the same tasks in the two species.

The corticopontine projection has been studied in a number of lower mammals, but most of the studies are not sufficiently detailed to permit a final comparison with the findings in cat and monkey. However, the overall pattern of termination in the rabbit (Abdel-Kader, 1968; Giolli and Guthrie, 1971) seems to be more like that in the cat, while in the armadillo (Harting and Martin, 1970), the opossum (Martin and King, 1968) and the tree shrew (Shriver and Noback, 1967) it appears to be more like that in the monkey. Further comparative studies may contribute to our understanding of the evolution of the cerebrocerebellar connections and the functional significance of the pontine nuclei and parts of the cerebellum.

SUMMARY

The corticopontine projection in the monkey has been studied by axonal degeneration techniques.

1. Quantitatively the most important contributions arise in the premotor region (area 6), the motor cortex (area 4, MI), somatic sensory cortex (areas 3, 1 and 2, SI), area 5 and parts of the visual cortex representing the peripheral visual field. Among these, MI appears to contribute most, while SI, area 5 and visual cortex probably send more fibres than area 6. A less heavy projection arises in area 7. Only relatively few fibres appear to emanate from parts of the visual cortex representing the central visual field, the prefrontal areas and the temporal lobe.

2. The corticopontine fibres terminate characteristically in sharply delimited slabs or lamella-like regions, extending as a rule rostrocaudally. Following large cortical lesions, the lamellæ appear to be more or less filled with terminal degeneration, while small lesions tend to produce numerous small patches. The density of degeneration within such patches does not increase substantially with increasing size of the lesions.

3. The various cortical regions project to a large extent on to separate parts of the pontine nuclei although considerable overlap may take place between some projection areas. The overall arrangement of terminal areas resembles somewhat the layers of an onion. MI and SI project in a central ‘core’, with fibres from MI distributed largely medial to those from SI. Area 6 projects to a thin lamella close to the midline and ventral aspect of the pons adjacent to the MI projection area. Area 5 appears to project lateral to SI, but probably with extensive overlap. Area 7 sends fibres to a thin sheet ventrolateral to area 5. Parts of the visual cortex representing central parts of the visual field supply a relatively small region rostrolaterally, while parts representing the peripheral visual field (shown in this study only for area 19) project on to a similarly situated area and in addition to regions

apparently supplied also from areas 5 and (probably) 7. The temporal cortex sends fibres to a small region dorsolaterally.

4. The projections from MI, SI and probably area 5, are somatotopically organized.

5. The organization of the corticopontine projection in the monkey is compared to that in the cat, as known from previous studies. The termination of fibres, often in several sharply delimited regions, is found in both species. The projections from the sensorimotor cortex terminate in roughly the same region in both, and the somatotopical patterns are similar. The projection areas of fibres from premotor, parietal and occipital areas, however, are very differently situated. This probably reflects differences in organization of cerebrocerebellar interconnections which presumably are of consequence for the use of the cerebellum in cat and monkey.

ACKNOWLEDGEMENTS

I would like to thank Professor C. G. Phillips for his encouragement and for the hospitality of the Department of Human Anatomy, Oxford. I am greatly indebted to Dr. T. P. S. Powell for so generously putting at my disposal the material used in the present study, and for helpful discussions at various stages of the work. This work was carried out when the author was a Wellcome/Jahre Travelling Research Fellow.

REFERENCES

ABDEL-KADER, G. A. (1968) The organization of the corticopontine system of the rabbit. *Journal of Anatomy*, **102**, 165-181.

ALBUS, K. and DONATE-OLIVER, F. (1977) Cells of origin of the occipitopontine projection in the cat: functional properties and intracortical location. *Experimental Brain Research*, **28**, 167-174.

ALLEN, G. I. and TSUKAHARA, N. (1974) Cerebrocerebellar communication systems. *Physiological Reviews*, **54**, 957-1006.

ASANUMA, H., FERNANDEZ, J., SCHEIBEL, M. E. and SCHEIBEL, A. B. (1974) Characteristics of projections from the nucleus ventralis lateralis to the motor cortex in cats: An anatomical and physiological study. *Experimental Brain Research*, **20**, 315-330.

ASTRUC, J. (1971) Corticofugal connections of area 8 (frontal eye field) in *Macaca mulatta*. *Brain Research, Amsterdam*, **33**, 241-256.

BAKER, J., GIBSON, A., GLICKSTEIN, M. and STEIN, J. (1976) Visual cells in the pontine nuclei of the cat. *Journal of Physiology, London*, **255**, 415-434.

BECK, E. (1950) Origin, course and termination of prefronto-pontine tract in the human brain. *Brain*, **73**, 368-391.

BRODAL, A. (1972) Cerebrocerebellar pathways. Anatomical data and some functional implications. *Acta Neurologica Scandinavica*, Suppl. 51, 153-196.

—— and COURVILLE, J. (1973) Cerebellar corticonuclear projection in the cat. Crus II. An experimental study with silver methods. *Brain Research, Amsterdam*, **50**, 1-23.

BRODAL, P. (1968*a*) The corticopontine projection in the cat. I. Demonstration of a somatotopically organized projection from the primary sensorimotor cortex. *Experimental Brain Research*, **5**, 210–234.

—— (1968*b*) The corticopontine projection in the cat. Demonstration of a somatotopically organized projection from the second somatosensory cortex. *Archives Italiennes de Biologie*, **106**, 310–332.

—— (1971*a*) The corticopontine projection in the cat. I. The projection from the proreate gyrus. *Journal of Comparative Neurology*, **142**, 127–140.

—— (1971*b*) The corticopontine projection in the cat. II. The projection from the orbital gyrus. *Journal of Comparative Neurology*, **142**, 141–152.

—— (1972*a*) The corticopontine projection from the visual cortex in the cat. I. The total projection and the projection from area 17. *Brain Research, Amsterdam*, **39**, 297–317.

—— (1972*b*) The corticopontine projection from the visual cortex in the cat. II. The projection from areas 18 and 19. *Brain Research, Amsterdam*, **39**, 319–335.

—— (1972*c*) The corticopontine projection in the cat. The projection from the auditory cortex. *Archives Italiennes de Biologie*, **110**, 119–144.

—— and WALBERG, F. (1977) The pontine projection to the cerebellar anterior lobe. An experimental study in the cat with retrograde transport of horseradish peroxidase. *Experimental Brain Research*, **29**, 233–248.

BRODMANN, K. (1909) *Vergleichende Lokalisationslehre der Grosshirnrinde*. Leipzig: J. A. Barth.

CAMPOS-ORTEGA, J. A., HAYHOW, W. R. and KLUVER, P. F. DE V. (1970) The descending projections from the cortical visual fields of *Macaca mulatta* with particular reference to the questions of a corticolateral geniculate pathway. *Brain Behavior and Evolution*, **3**, 368–414.

CASAGRANDE, V. A. and HARTING, J. K. (1975) Transneuronal transport of tritiated proline in the visual pathways of the tree shrew *Tupaia glis*. *Brain Research, Amsterdam*, **96**, 367–372.

CONRAD, B. and BROOKS, V. B. (1974) Effects of dentate cooling on rapid alternating arm movements. *Journal of Neurophysiology*, **37**, 792–804.

COULTER, J. D., EWING, L. and CARTER, C. (1976) Origin of primary sensorimotor cortical projections to lumbar spinal cord of cat and monkey. *Brain Research, Amsterdam*, **103**, 366–372.

—— and JONES, E. G. (1977) Differential distribution of corticospinal projections from individual cytoarchitectonic fields in the monkey. *Brain Research, Amsterdam*, **129**, 335–340.

COURVILLE, J., DIAKIW, N. and BRODAL, A. (1973) Cerebellar corticonuclear projection in the cat. The paramedian lobule. An experimental study with silver methods. *Brain Research, Amsterdam*, **50**, 25–45.

DE VITO, J. L. and SMITH, O. A. Jr. (1964) Subcortical projections of the prefrontal lobe of the monkey. *Journal of Comparative Neurology*, **123**, 413–424.

DOW, R. S. (1942) Cerebellar action potentials in response to stimulation of the cerebral cortex in monkeys and the cat. *Journal of Neurophysiology*, **5**, 121–136.

ECCLES, J. C., SABAH, N. H., SCHMIDT, R. F. and TÁBOŘÍKOVÁ, H. (1972) Mode of operation of the cerebellum in the dynamic loop control of movement. *Brain Research, Amsterdam*, **40**, 73–80.

EVARTS, E. V. and THACH, W. T. (1969) Motor mechanisms of the CNS: cerebrocerebellar interrelations. *Annual Review of Physiology*, **31**, 451–498.

FINK, R. P. and HEIMER, L. (1967) Two methods for selective silver impregnation of degenerating axons and their synaptic endings in the central nervous system. *Brain Research, Amsterdam*, **4,** 369-374.

GIOLLI, R. A. and GUTHRIE, M. D. (1971) Organization of subcortical projection of visual areas I and II in the rabbit. *Journal of Comparative Neurology*, **142,** 351-376.

GOLDMAN, P. S. and NAUTA, W. J. H. (1976) Autoradiographic demonstration of a projection from prefrontal association cortex to the superior colliculus in the rhesus monkey. *Brain Research, Amsterdam*, **116,** 145-149.

HARTING, J. K. and MARTIN, G. F. (1970) Neocortical projections to the pons and medulla of the nine banded armadillo. *Journal of Comparative Neurology*, **138,** 483-500.

HARVEY, R. J., PORTER, R. and RAWSON, J. A. (1977) The natural discharges of Purkinje cells in paravermal regions of lobules V and VI of the monkey's cerebellum. *Journal of Physiology, London*, **271,** 515-536.

HODDEVIK, G. H. (1975) The pontocerebellar projection on to the paramedian lobule in the cat: An experimental study with the use of horseradish peroxidase as a tracer. *Brain Research, Amsterdam*, **95,** 291-307.

—— BRODAL, A., KAWAMURA, K. and HASHIKAWA, T. (1977) The pontine projection to the cerebellar vermal visual area studied by means of the retrograde axonal transport of horseradish peroxidase. *Brain Research, Amsterdam*, **123,** 209-227.

HOLMES, G. (1939) The cerebellum of man. *Brain*, **62,** 1-30.

ITO, M. (1970) Neurophysiological aspects of the cerebellar motor control system. *International Journal of Neurology*, **7,** 162-176.

JONES, E. G. and POWELL, T. P. S. (1969) Connexions of the somatic sensory cortex of the rhesus monkey. II. Contralateral cortical connexions. *Brain*, **92,** 717-730.

—— —— (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, **93,** 793-820.

—— and WISE, S. P. (1977) Size, laminar and columnar distribution of efferent cells in the sensory-motor cortex of monkeys. *Journal of Comparative Neurology*, **175,** 391-438.

KAWAMURA, K. and BRODAL, A. (1973) The tectopontine projection in the cat: An experimental anatomical study with comments on pathways for teleceptive impulses to the cerebellum. *Journal of Comparative Neurology*, **149,** 371-390.

KEMP, J. and POWELL, T. P. S. (1970) The cortico-striate projection in the monkey. *Brain*, **93,** 525-546.

KÜNZLE, H. and AKERT, K. (1977) Efferent connections of cortical area 8 (frontal eye field) in *Macaca fascicularis* A reinvestigation using the autoradiographic technique. *Journal of Comparative Neurology*, **173,** 147-163.

KUYPERS, H. G. J. M. (1958) Some projections from the pericentral cortex to the pons and lower brain stem in monkey and chimpanzee. *Journal of Comparative Neurology*, **110,** 221-252.

—— (1960) Central cortical projections to motor and somatosensory cell groups. An experimental study in the rhesus monkey. *Bram*, **83,** 161-184.

—— and LAWRENCE, D. G. (1967) Cortical projections to the red nucleus and the brain stem in the rhesus monkey. *Bram Research, Amsterdam*, **4,** 151-188.

LYNCH, J. C., MOUNTCASTLE, V. B., TALBOT, W. H. and YIN, T. C. T. (1977) Parietal lobe mechanisms for directed visual attention. *Journal of Neurophysiology*, **40**, 362–389.

MARTIN, G. F. and KING, J. S. (1968) The basilar pontine gray of the opossum (*Didelphis virginiana*). II. Experimental determination of neocortical input. *Journal of Comparative Neurology*, **133**, 447–462.

METTLER, F. A. (1935) Corticofugal fiber connections of the cortex of *Macaca mulatta*. The occipital region. *Journal of Comparative Neurology*, **61**, 221–256.

MIZUNO, N., MOCHIZUKI, K., MATSUSHIMA, C. A. R. and SASAKI, K. (1973) Projections from the parietal cortex to the brain stem nuclei in the cat, with special reference to the parietal cerebro-cerebellar system. *Journal of Comparative Neurology*, **147**, 511–522.

MOUNTCASTLE, V. B., LYNCH, J. C., GEORGOPOULOS, A., SAKATA, H. and ACUNA, C. (1975) Posterior parietal association cortex of the monkey: Command functions for operations within extrapersonal space. *Journal of Neurophysiology*, **38**, 871–908.

MÜLLER-PREUSS, P. and JÜRGENS, U. (1976) Projections from the 'cingular' vocalization area in the squirrel monkey. *Brain Research, Amsterdam*, **103**, 29–43.

NAUTA, W. J. H. and GYGAX, P. A. (1954) Silver impregnation of degenerating axons in the central nervous system: a modified technic. *Stain Technology*, **29**, 91–93.

NYBY, O. and JANSEN, J. (1951) An experimental investigation of the corticopontine projection in *Macaca mulatta. Skrifter utgitt av Det Norske Videnskaps-Akademi i Oslo. I. Mat.-Naturv. Klasse 1951*, 1–47.

OKA, H., SASAKI, K., MATSUDA, Y., YASUDA, T. and MIZUNO, N. (1975) Responses of pontocerebellar neurones to stimulation of the parietal association and the frontal motor cortices. *Brain Research, Amsterdam*, **93**, 399–407.

PEARSON, R. C. A. and POWELL, T. P. S. (1978) The cortico-cortical connections to area 5 of the parietal lobe from the primary somatic sensory cortex of the monkey. *Proceedings of the Royal Society of London, B*, **200**, 103–108.

POWELL, T. P. S. (1973) Sensory convergence in the cerebral cortex. In: *Surgical Approaches in Psychiatry*, edited by L. V. Laitinen and K. E. Livingston. Lancaster: Medical and Technical Publishing Company, pp. 266–281.

RISPAL-PADEL, L. and GRANGETTO, A. (1977) The cerebello-thalamo-cortical pathway. Topographical investigation at the unitary level in the cat. *Experimental Brain Research*, **28**, 101–123.

RÜEGG, D. and WIESENDANGER, M. (1975) Corticofugal effects from sensorimotor area I and somatosensory area II on neurones of the pontine nuclei in the cat. *Journal of Physiology, London*, **247**, 745–757.

RUSSEL, J. R. and DE MYER, W. (1961) The quantitative cortical origin of pyramidal axons of *Macaca* rhesus, with some remarks on the slow rate of axolysis. *Neurology, Minneapolis*, **11**, 96–108.

SASAKI, K., KAWAGUCHI, S., OKA, H., SAKAI, M. and MIZUNO, N. (1976) Electrophysiological studies on the cerebello-cerebral projections in monkeys. *Experimental Brain Research*, **24**, 495–507.

—— OKA, H., KAWAGUCHI, S., JINNAI, K. and YASUDA, T. (1977) Mossy and climbing fibre responses produced in the cerebellar cortex by stimulation of the cerebral cortex in monkeys. *Experimental Brain Research*, **29**, 419–428.

SHRIVER, J. E. and NOBACK, C. R. (1967) Cortical projections to the lower brain stem and spinal cord in the tree shrew (*Tupaia glis*). *Journal of Comparative Neurology*, **130**, 25–54.

SNIDER, R. S. and ELDRED, E. (1952) Cerebro-cerebellar relations in the monkey. *Journal of Neurophysiology*, **15**, 27-40.

SPATZ, W. B., TIGGES, J. and TIGGES, M. (1970) Subcortical projections, cortical associations, and some intrinsic interlaminar connections of the striate cortex in the squirrel monkey. *Journal of Comparative Neurology*, **140**, 155-174.

STRICK, P. L. (1976) Anatomical analysis of ventrolateral thalamic input to primate motor cortex. *Journal of Neurophysiology*, **39**, 1020-1031.

SUNDERLAND, S. (1940) The projection of the cerebral cortex on the pons and cerebellum in the macaque monkey. *Journal of Anatomy*, **74**, 201-226.

TALBOT, S. A. and MARSHALL, W. H. (1941) Physiological studies on neural mechanisms of visual localization and discrimination. *American Journal of Ophthalmology*, **24**, 1255-1264.

TOMASCH, J. (1968) The overall information capacity of the major afferent and efferent cerebellar cell and fiber systems. *Confinia Neurologica*, **30**, 359-367.

WHITLOCK, D. G. and NAUTA, W. J. H. (1956) Subcortical projections from the temporal neocortex in *Macaca mulatta. Journal of Comparative Neurology*, **106**, 183-212.

WIESENDANGER, M., SÉGUIN, J. J. and KÜNZLE, H. (1974) The supplementary motor area—a control system for posture? *Advances in Behavioral Biology*, **7**, 331-346.

WIITANEN, J. T. (1969) Selective silver impregnation of degenerating axons and axon terminals in the central nervous system of the monkey. *Brain Research, Amsterdam*, **14**, 546-548.

WISE, S. P. and JONES, E. G. (1977) Cells of origin and terminal distribution of descending projections of the rat somatic sensory cortex. *Journal of Comparative Neurology*, **175**, 129-158.

WOOLSEY, C. N. (1958) Organization of somatic sensory and motor areas of the cerebral cortex. In: *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey. Madison: University of Wisconsin Press, pp. 63-81.

(*Received November 1, 1977*)

Brain (1978), **101**, 285-294

LATE BLINK REFLEX CHANGES IN LATERAL MEDULLARY LESIONS

AN ELECTROPHYSIOLOGICAL AND NEURO-ANATOMICAL STUDY OF WALLENBERG'S SYNDROME

by B. W. ONGERBOER DE VISSER *and* H. G. J. M. KUYPERS

(*From the Departments of Neurology and Clinical Neurophysiology of the Municipal Hospital, Slotervaart, Amsterdam, and the Department of Anatomy, Erasmus University, Rotterdam, The Netherlands*)

INTRODUCTION

REFLEX blinking evoked by a tap on one side of the forehead was first described by Overend in 1896, and the electromyographic investigation of this reflex was first undertaken by Kugelberg in 1952. The substitution of supra-maximal electrical stimulation of the supra-orbital nerve for the mechanical tap led to standardization of the technique.

The clinical value of registration of the blink reflex is known from several reports (Rushworth, 1962; Kimura, 1973; Ongerboer de Visser and Goor, 1974; Goor and Ongerboer de Visser, 1976). The reflex movements evoked in the orbicularis oculi muscles by electrical stimulation of the supra-orbital nerve have two components: an early oligosynaptic ipsilateral response and a late polysynaptic bilateral response. The common afferent limb of this reflex is formed by the sensory root of the trigeminal nerve, the facial nerve is the efferent limb. There are indications that the early blink response is conducted through the pons and relayed via neurons at the level of the principal sensory nucleus of the fifth nerve (Tokunaga, Oka, Murao, Yokoi, Okumara, Hirata, Miyashita and Yoshitatsu, 1958; Namerow, 1970; Kimura, 1975). From findings in patients who have undergone a tractotomy of the fifth nerve (Sjöquist operation, Kugelberg, 1952) and in patients with Wallenberg's lateral medullary syndrome (Kimura and Lyon, 1972) with involvement of the spinal trigeminal tract and its nucleus, it may be concluded that the fibres of the first-order neurons which are responsible for the late component of the reflex terminate in the area of the ipsilateral spinal trigeminal nucleus. However, adequate data concerning connections from this nucleus to the ipsilateral and contralateral facial nuclei in man are not yet available.

The present communication reports effects of lateral medullary vascular lesions on the late component of the blink reflex.

The late bilateral component of the blink reflex is important for the differentiation between lesions of the fifth cranial nerve or the spinal trigeminal tract and those of the seventh cranial nerve (Kimura and Lyon, 1972; Goor and Ongerboer de Visser, 1976). Thus, a bilateral delay in the late component of the reflex or its absence (afferent delay or block) following stimulation of the supra-orbital nerve on the affected side suggests a lesion of the trigeminal nerve or spinal trigeminal tract. On the other hand, a unilateral delay or absence of the late reflex (efferent delay or block) on the affected side after stimulation of the supra-orbital nerve on either side suggests a facial nerve lesion.

METHODS

The technique used to record the blink reflex and its components is described elsewhere (Kimura, Powers and van Allen, 1969; Ongerboer de Visser and Goor, 1974). Reflex responses in the orbicularis oculi muscles were recorded by coaxial needle electrodes. A difference in latency between the right and left sides exceeding 1·5 ms for the early reflex and 8·0 ms for the late reflex was considered abnormal (Ongerboer de Visser and Goor, 1974).

In the present study the blink reflex was investigated in 13 noncomatose patients ranging in age from 45 to 79 years, who showed clinical signs and symptoms of the Wallenberg syndrome (Currier, Giles and De Jong, 1961; Fisher, Karnes and Kubik, 1961). Of these 13 patients, 4 (Group 1) had the typical syndrome consisting of loss of pain and temperature sensation on the ipsilateral half of the face and on the contralateral trunk and limbs, ipsilateral hemiataxia, ipsilateral Horner's syndrome, and nystagmus. These patients had the most severe degree of vertigo, nausea, vomiting, dysphonia, dysphagia, imbalance, and hiccups. Two of them also complained of pain in the face and body. One of these 4 patients had a tumour (ependymoma) situated in the left cerebellopontine angle, combined with an ischæmic lesion in the lateral part of the medulla oblongata. One month after the development of the Wallenberg syndrome the patient developed encephalomalacia on the left side, due to occlusion of the middle cerebral artery, and died three months later of bronchopneumonia.

In 6 (Group 2) of the 13 patients, dysphonia, dysphagia, nausea and vomiting were less severe than in Group 1. However, Horner's syndrome, the cerebellar signs, nystagmus, and loss of pain sensation in the face and the contralateral trunk were present. In the remaining 3 (Group 3) of the 13 patients, vertigo, nausea and vomiting lasted only one day. In 2 of them pain sensation was slightly diminished in the ipsilateral half of the face and the contralateral side of the trunk. The third patient showed no sensory disturbances on the trunk and the cerebellar signs were minimal, but Horner's syndrome was present ipsilaterally.

All the patients were examined electrophysiologically within the first week after the onset of the symptoms. An autopsy was performed in 3 cases. The findings verified the clinical diagnosis, and an infarct was found in the dorsolateral region of the medulla oblongata. The ischæmic lesion of the patient with the cerebello-pontine tumour was investigated in detail.

RESULTS

The latencies of the early components of the blink reflex fell within the normal range in all 13 cases. This was taken to indicate that the first branch of the fifth cranial nerve and the second branch of the seventh cranial nerve were intact and the pontine trigeminal-facial reflex arc was functioning normally (Namerow, 1970; Kimura, 1975; Goor and Ongerboer de Visser, 1976).

The latencies of the late component were normal in only 2 patients, both of whom showed a slight facial hypalgesia. In the remaining 11 cases late reflexes were abnormal. In these 11 cases three different types of abnormality were found. The first type (A), which was present in 3 cases, consisted of a bilateral delay in the late response (fig. 1), ranging between 10 and 16 ms. The second type (B) was seen in 5 cases and consisted of a bilateral absence of the late response (fig. 2) upon stimulation of the supra-orbital nerve on the side of the lesion. Stimulation of the supra-orbital nerve on the unaffected side in both sets of patients produced a normal response in the orbicularis oculi muscle on both sides. The third type (C) (fig. 3) was found in 3 cases. In these cases stimulation of the nerve on the affected side failed to elicit a bilateral late reflex response and stimulation of the nerve on the unaffected side only elicited a late response on that side but not on the affected side.

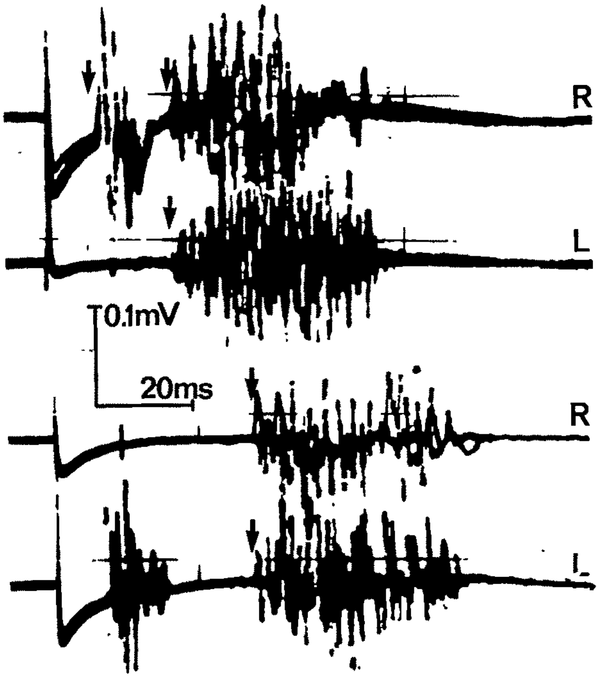


FIG 1. Example of the Type A abnormality of the late blink reflex. In this case the lesion is on the left side. *Upper pair* of traces, normal blink reflex after stimulation of the right supra-orbital nerve. *Lower pair* of traces, afferent delay of the late blink reflex after stimulation of the left supra-orbital nerve ipsilateral to the lesion.

The 3 patients with the Type C abnormality belonged to Group 1 with the most severe symptoms. In one of these cases the lesion was investigated in detail. In this patient, who had a tumour in the left cerebellopontine angle, a lateral medullary

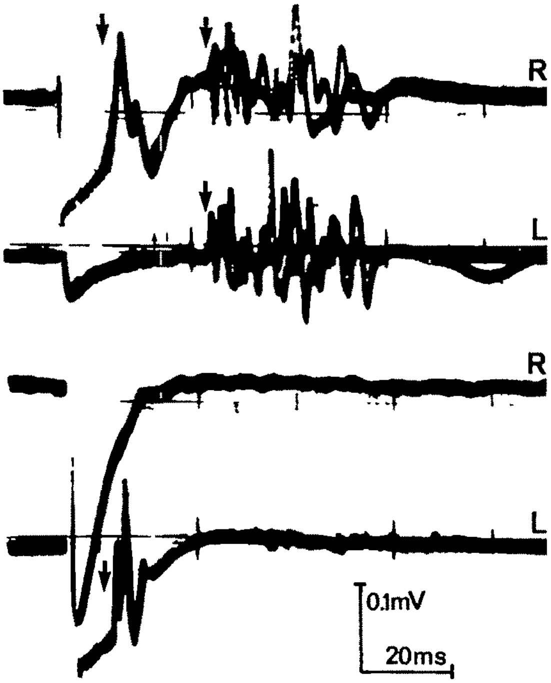


FIG. 2. Example of the Type B abnormality of the late blink reflex. In this case the lesion is on the left side. *Upper pair* of traces, normal blink reflex after stimulation of the right supra-orbital nerve *Lower pair* of traces, afferent block of the late blink reflex after stimulation of the left supra-orbital nerve ipsilateral to the lesion.

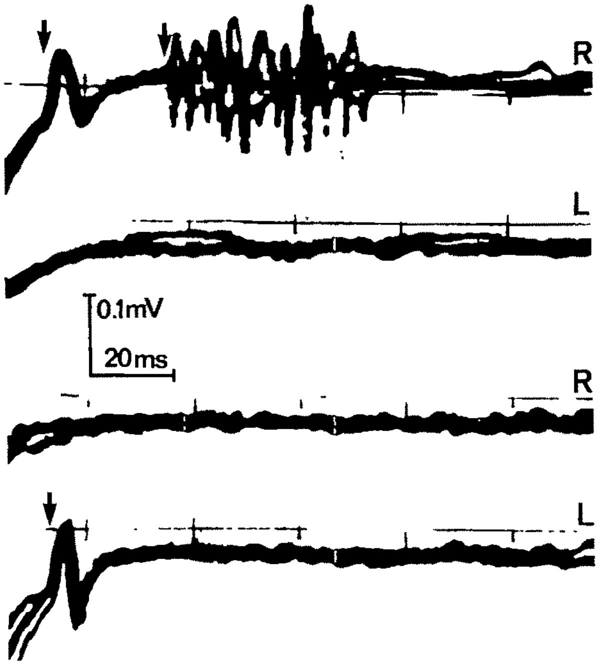


FIG. 3. Example of the Type C abnormality of the late blink reflex. *Upper pair* of traces, normal late response on the right (the intact side) and an absence of the late response on the left (the side of the lesion) after stimulation of the right supra-orbital nerve. *Lower pair* of traces, afferent block of the late blink reflex after stimulation of the left supra-orbital nerve ipsilateral to the lesion.

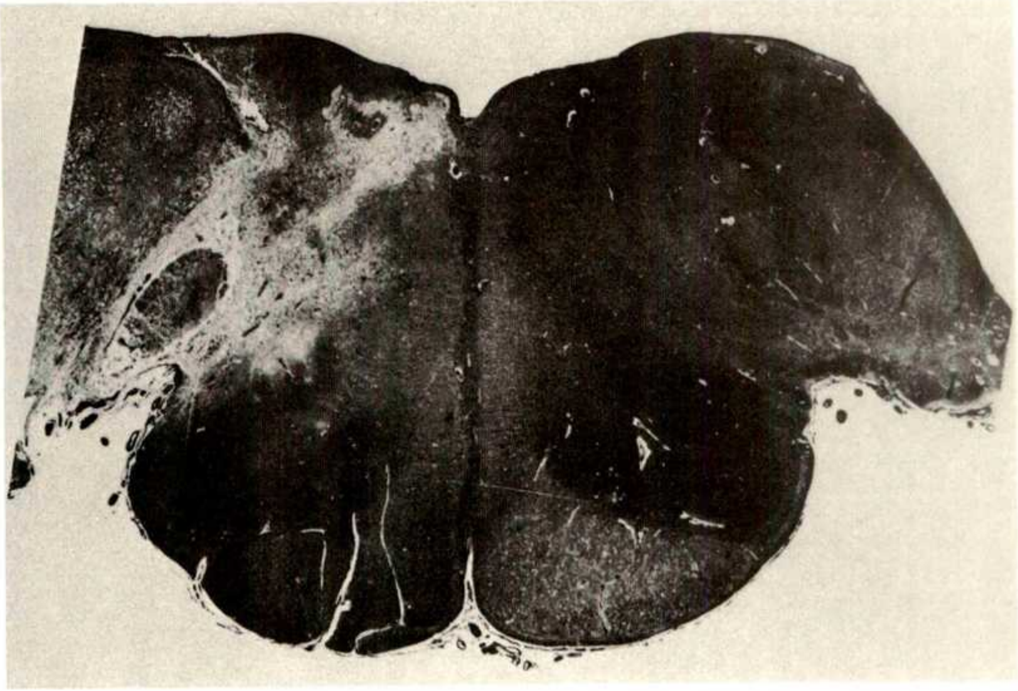


FIG. 4. Cross-section through the medulla oblongata showing the unilateral infarction in the lateral part of the medulla oblongata in our Type C case. Note that the infarction involves mainly the spinal fifth nerve complex, its tract, and the lateral reticular formation. (Mallory ×3; by courtesy of Dr. G. Th. A. M. Bots, University Hospital, Leiden).

infarct was found on the same side as the tumour (fig. 4). This infarct was spindle-shaped in the rostrocaudal direction and extended from the level of the obex to the level of the pontomedullary junction (fig. 5). At the level of the obex the infarct was rather narrow and involved the spinal trigeminal complex and its descending tract, as well as the laterally adjacent band of fibres of the inferior cerebellar peduncle. Further rostrally the infarct was wider and also involved the vestibular complex, the bulbar lateral reticular formation, and the adjoining area along the ventral aspect of the medulla oblongata, that is, lateral to the inferior olive. The medial reticular formation was largely unaffected. At the level of the hypoglossal nuclei the infarct extended medially as far as the fibres of the hypoglossal nerve, but did not involve this nerve or its motor nucleus. At the level of the pontomedullary junction the infarct became narrower and lay immediately lateral to the facial nucleus, thus involving the spinal trigeminal complex and the lateral portion of the bulbar reticular formation.

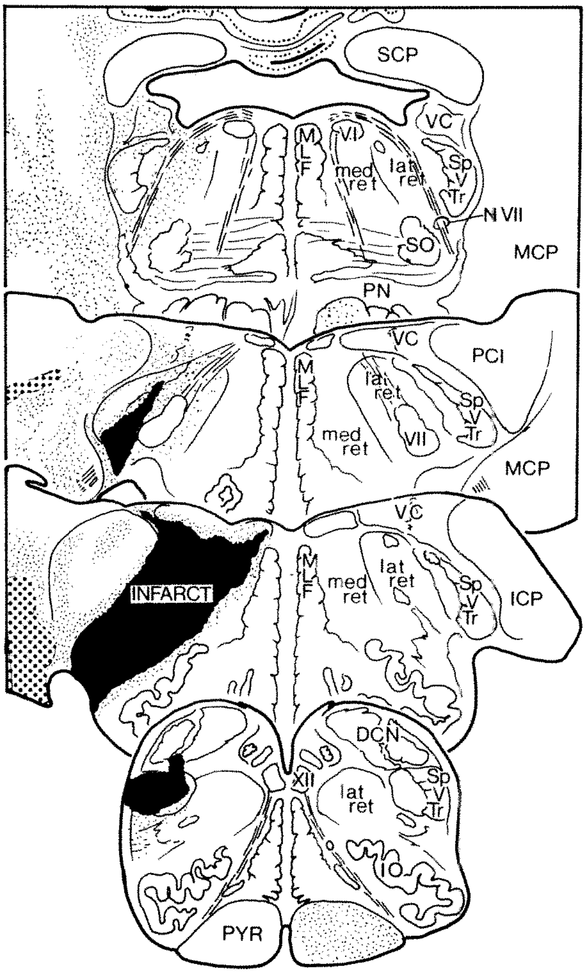


FIG. 5. Semi-diagrammatic representation of the location and extent of the infarction in the medulla oblongata investigated in detail. *Large dots* indicate the position of the tumour (ependymoma); *fine dots*, the area of fibre degeneration. The degeneration in the pyramidal tract on the right was caused by the encephalomalacia which developed two months before the patient's death.

Vm = trigeminal motor nucleus. Vp = trigeminal principal sensory nucleus. SpVTr = spinal trigeminal tract. SpVCo = spinal trigeminal complex. VI = abducens nucleus. VII = facial nucleus. NVII = facial nerve. XII = hypoglossal nucleus. MLF = medial longitudinal fasciculus. Med. ret. = medial reticular formation. Lat. ret. = lateral reticular formation. VC = vestibular complex. SO = superior olivary complex. Pyr = pyramidal tract. SCP = superior cerebellar peduncle. MCP = middle cerebellar peduncle. PCI = inferior cerebellar peduncle. PN = pontine nuclei. DCM = dorsal column nuclei.

DISCUSSION

The electrophysiological findings of early reflex responses within the normal range and a bilateral delay (Type A, fig. 1) or absence (Type B, fig. 2) of the late reflex response upon stimulation of the nerve on the affected side are consistent with earlier observations in 7 patients with the Wallenberg syndrome reported by Kimura and Lyon (1972). Of special interest in this respect is the Type C abnormality (fig. 3), which had not been reported previously. This abnormality occurred in 3 of the 4 patients belonging to Group 1, that is, with the most severe symptoms. In view of the anatomical findings in one of these patients (figs. 4 and 5), they all probably had rather extensive lesions. This strongly suggests that when the Type C abnormality occurs in Wallenberg's syndrome the lesion can be expected to extend deeply into the medulla oblongata.

With respect to the distribution of the fibre connections underlying the bilateral late response of the blink reflex the present findings lead to the following conclusions. The route by which the bilateral late reflex response is established involves the ipsilateral spinal trigeminal tract and the area of the ipsilateral spinal trigeminal nucleus (fig. 6). This is based on the fact that in the cases with A and B abnormalities

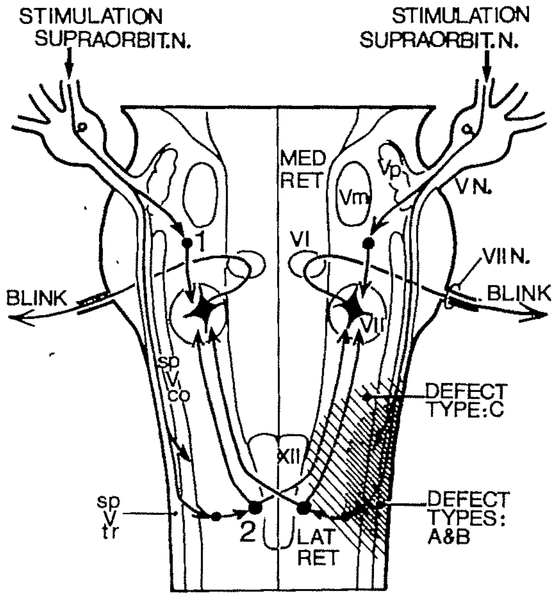


FIG. 6 Diagram showing the presumed location of the bulbar interneurons subserving the two components of the blink reflex: (1) interneurons subserving the ipsilateral early component; (2) interneurons subserving the bilateral late component. A lesion involving the double-shaded area on the right would only interfere with the bilateral late component elicited by stimulation of the nerve on the affected side. A larger lesion also involving the lightly shaded area would also interfere with the late component on the affected side elicited by stimulation of the nerve on the intact (left) side. For key to abbreviations *see* legend to fig. 5.

a normal bilateral late reflex response could still be elicited upon stimulation of the nerve on the intact side. In the cases with the Type C abnormality the bilateral late response was absent when stimulation of the nerve was applied to the affected side as in the cases with Type B abnormality. When the nerve on the intact side was stimulated, however, a normal late response was only observed on the intact side and no late response occurred on the affected side. This leads to two conclusions. First, the late response on the stimulated side is conducted via an ipsilateral ascending medullary pathway which leads from the area of the spinal trigeminal nucleus to the ipsilateral facial nucleus (fig. 6). Secondly, because of the absence of the late response on the affected side upon stimulation of the nerve on the intact side, the contralateral late response must be established by way of an ascending medullary pathway which crosses the midline in the caudal medulla oblongata before ascending to the contralateral facial nucleus (fig. 6). The fact that the lesion in the case with the ependymoma in the cerebello-pontine angle involved the bulbar lateral reticular formation but largely spared the medial reticular formation (fig. 5) suggests that the ipsilaterally and the contralaterally ascending medullary pathways to the facial nuclei are located in the lateral reticular formation of the lower brain-stem.

With respect to the above-mentioned conclusions it is of interest to note that according to Holstege and Kuypers (1977) and Holstege, Kuypers and Dekker (1977), the bulbar lateral reticular formation in the cat contains a lateral and a medial propriobulbar fibre system; the former distributes fibres to the bulbar motor nuclei mainly ipsilaterally, whereas the latter tends to distribute fibres to these nuclei bilaterally. The medial propriobulbar system also contains fibres arising from neurons at the level of the obex and passing to the intermediate facial subnucleus on both sides. This subnucleus is believed to innervate the orbicularis oculi muscle (Courville, 1966). If these connections found in the cat also exist in man, they could explain the Type C abnormality, because the trigemino-reticular lesion would not only block the trigeminal access route to the caudal medullary neurons on the affected side, which project to motoneurons of the orbicularis oculi muscle on both sides, but would also interrupt the crossed ascending fibres which are distributed from the corresponding neurons on the intact side to the motoneurons of the orbicularis oculi muscle on the affected side.

From the clinical point of view it may be concluded from the present study that recording of the late blink reflex has value, because the results may provide the clinician with further information about the extent of the brain-stem lesion.

SUMMARY

In 13 patients with Wallenberg's lateral medullary syndrome, blink reflexes elicited by electrical stimulation of the supra-orbital nerve were investigated. The early response of the reflex was normal in all of the patients, but the late blink reflex responses showed three types of abnormality. Type A consisted of a bilateral

delay (fig. 1), and Type B of a bilateral absence of the late reflex response (fig. 2) to stimulation on the affected side in combination with a normal late reflex response on both sides when the normal side was stimulated. Type C, which was seen in 3 cases, consisted of a bilateral absence of the late reflex response upon the stimulation of the affected side, in combination with a normal late response on the intact side and absence of the late response on the affected side when the unaffected side was stimulated (fig. 3).

It is concluded that the late reflex is conducted via medullary pathways running both ipsilaterally and contralaterally to the stimulated side before making connection with the ipsilateral and the contralateral facial nucleus, respectively. In one of the cases with the Type C abnormality, detailed investigation showed involvement of the descending trigeminal tract, its nucleus, and the lateral reticular formation. The facial nerve and nucleus were largely spared. This finding suggests that for the late blink reflex the ascending medullary pathway from the spinal fifth nerve complex to the facial nuclei are located in the lateral reticular formation of the lower brain-stem. In addition, the finding of the Type C abnormality in cases with severe symptoms of the Wallenberg syndrome indicates a lesion extending medially beyond the fifth nerve complex.

ACKNOWLEDGEMENTS

This study was begun in the Departments of Neurology and Clinical Neurophysiology of the Leyenburg Hospital in The Hague and was continued in the corresponding departments of the Leiden and Rotterdam (Dijkzigt) University Hospitals and the Slotervaart Hospital in Amsterdam.

The authors wish to thank all those whose co-operation made the study possible, as well as Dr. D. Moffie for his critical reading of the manuscript.

Reprint requests to Dr. B. W. Ongerboer de Visser, Department of Neurology, Slotervaart Hospital, Louwesweg, Amsterdam.

REFERENCES

COURVILLE, J. (1966) The nucleus of the facial nerve: the relation between cellular groups and peripheral branches of the nerve. *Brain Research, Amsterdam,* **1,** 338–354.

CURRIER, R. D., GILES, C. L. and DE JONG, R. N. (1961) Some comments on Wallenberg's lateral medullary syndrome. *Neurology, Minneapolis,* **2,** 778–791.

FISHER, C. M., KARNES, W. E. and KUBIK, C. S. (1961) Lateral medullary infarction—the pattern of vascular occlusion. *Journal of Neuropathology and Experimental Neurology,* **20,** 323–379.

GOOR, C. and ONGERBOER DE VISSER, B. W. (1976) Jaw and blink reflexes in trigeminal nerve lesions, an electro-diagnostic study. *Neurology, Minneapolis,* **26,** 95–97.

HOLSTEGE, G. and KUYPERS, H. G. J. M. (1977) Propriobulbar fibre connections to trigeminal, facial and hypoglossal motor nuclei. I. An anterograde degeneration study in the cat. *Brain,* **100,** 239–264.

—— —— and DEKKER, J. J. (1977) The organization of the bulbar connections to the trigeminal, facial and hypoglossal motor nuclei. II. An autoradiographic tracing study in cat. *Brain,* **100,** 265–286.

KIMURA, J. (1973) The blink reflex as a test for brain-stem and higher central nervous system function. In: *New Developments in Electromyography and Clinical Neurophysiology*. Edited by J. E. Desmedt. Basel: Karger, Vol. 3, pp. 682–691.

—— (1975) Electrically elicited blink reflex in diagnosis of multiple sclerosis. *Brain*, **98**, 413–426.

—— POWERS, J. M. and VAN ALLEN, M. W. (1969) Reflex response of orbicularis oculi muscles to supra-orbital nerve stimulation. *Archives of Neurology*, **21**, 193–199

—— and LYON, L. W. (1972) Orbicularis oculi reflex in the Wallenberg syndrome: alteration of the late reflex by lesions of the spinal tract and nucleus of the trigeminal nerve. *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 228–233.

KUGELBERG, E. (1952) Facial reflexes. *Brain*, **75**, 385–396.

NAMEROW, N. S. (1970) The orbicularis oculi reflex in multiple sclerosis. *Neurology, Minneapolis*, **20**, 1200–1203.

ONGERBOER DE VISSER, B. W. and GOOR, C. (1974) Electromyographic and reflex study in idiopathic and symptomatic trigeminal neuralgias: latency of the jaw and blink reflexes. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 1225–1230.

OVEREND, W. (1896) Preliminary note on a new cranial reflex. *Lancet*, **i**, 619.

RUSHWORTH, G. (1962) Observations on blink reflexes. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 95–108.

TOKUNAGA, A., OKA, M., MURAO, T., YOKOI, H., OKUMARA, T., HIRATA, T., MIYASHITA, Y. and YOSHITATSU, S. (1958) An experimental study on facial reflex by evoked electromyography. *Medical Journal of Osaka University*, **9**, 397–411.

(Received November 8, 1977)

Brain (1978), **101**, 295–305

THE SENSATION OF HEAVINESS AFTER SURGICAL DISCONNECTION OF THE CEREBRAL HEMISPHERES IN MAN

by S. C. GANDEVIA

(*From the School of Physiology and Pharmacology, University of New South Wales, P.O. Box 1, Kensington, 2033, Sydney, N.S.W., Australia*)

SURGICAL disconnection of the cerebral hemispheres does not produce gross impairment of bimanual motor co-ordination in monkeys (Mark and Sperry, 1968) or man (Sperry, 1966, 1974) although interconnections between the motor cortical systems controlling the left and right limbs are severed. The loss of interhemispheric communication is shown, for example, by the inability of patients to describe unusual objects presented to the non-dominant hand or visual material shown to the non-dominant half-field (*see* Sperry, 1966; Sperry, Gazzaniga and Bogen, 1969). Some somæsthetic information can be perceived by the hemisphere ipsilateral to the stimulus as patients are able to make a verbal detection of cutaneous, thermal and painful stimuli presented on the left side (Sperry, 1966; Sperry *et al.*, 1969; Levy and Sperry, 1970; Gazzaniga, 1970). Simple proprioceptive information arising in joints and skin, and also in muscles, was shown by McCloskey (1973) to be distributed to both hemispheres. Despite the access of one hemisphere to proprioceptive information from both sides of the body, split-brain patients are unable to mimic with one hand complex postures imposed on the fingers and hand of the other side, nor are they able to retrieve from an array of objects with one hand an object similar to one held in the other hand (*see* Sperry, 1966; Sperry *et al.*, 1969). Although anatomical studies have not revealed a strong transcallosal connection between the primary somatic cortex in each hemisphere for distal parts of the limb (Jones and Powell, 1969; Jones, Burton and Porter, 1975; cf. Shanks, Rockel and Powell, 1975) an electrophysiological study of single fibres within the corpus callosum of the cat revealed that information from the distal forelimb was transmitted through the callosum (Innocenti, Manzoni and Spidalieri, 1972, 1974).

Detailed studies on the sensation of heaviness have not been reported for human split-brain patients. Akelaitis (1944) reported from a study of patients with surgical disconnection of the hemispheres that no impairment in weight discrimination occurred. Gazzaniga (1970) briefly noted that afferent information signalling heaviness may be conveyed to the ipsilateral hemisphere, but suggested that the information signals the tactile qualities of the object being lifted. Nebes and Sperry (1971) found that interhemispheric comparisons of weight were possible in a patient with disconnection of the cerebral hemispheres and additional birth injury in the dominant hemisphere. This ability was ascribed to the use of paths conveying tactile information to the ipsilateral hemisphere. These studies imply either that ascending afferents have both ipsilateral and crossed projections to the cerebral hemispheres or that commissural connections 'below' the level of the corpus callosum distribute afferent inputs to both hemispheres. Studies on man and monkeys following hemidecortication (Fulton, 1943) and hemispherectomy in monkeys (White, Schreiner, Hughes, MacCarty and Grindlay, 1959) confirm the presence of functional ipsilateral paths. Fulton suggested that there is bilateral projection of cutaneous afferents but only unilateral projection of proprioceptive information. The observations of Penfield and Rasmussen (1950) support this suggestion as they found loss of sensation of movement and position in the contralateral limb of patients after removal of the postcentral gyrus, while significant cutaneous sensibility was retained.

Recent studies have shown that in making estimates of the perceived heaviness of a lifted object normal subjects rely on sensing the effort or outgoing voluntary motor command, preferring this to tactile or intramuscular signals of achieved tension (McCloskey, Ebeling and Goodwin, 1974; Gandevia and McCloskey, 1977*a*, *b*, *c*). An increase in the perceived heaviness of a lifted object occurs whenever the lifting muscle is weakened, irrespective of how the weakness is produced: by muscular fatigue; by partial curarization; by inhibition of the lifting motoneurons by activating muscle spindles of the antagonist; or by neurological disorders (unilateral cerebellar hypotonia, Holmes, 1917; simple motor strokes, Gandevia and McCloskey, 1977*a*). While subjects prefer to use signals related to the effort used, as they do when weakened, they are able under some circumstances to attend to signals of achieved tension, if requested to do so (McCloskey *et al.*, 1974; Gandevia and McCloskey, 1977*b*; Roland and Ladegaard-Pedersen, 1977).

This study was designed to see, first, if split-brain patients could accurately match lifted weights, and secondly, to see whether they used the size of the voluntary motor command to estimate the heaviness of objects lifted by a distal muscle or if they relied on peripheral signals of achieved force or cutaneous pressure which seem to be distributed to both hemispheres. The split-brain patients, like normal subjects, sensed the motor command being used as an indicator of heaviness; information about this command or effort seemed to be available to both hemispheres.

METHODS

Patients

Three patients of Drs. P. J. Vogel and J. E. Bogen (L.B., N.G. and N.W.) were examined during August, 1977. They had all undergone surgical division of the forebrain commissures, including the entire corpus callosum and the anterior commissure as part of treatment for severe epileptic seizures uncontrolled by medication. The hippocampal commissure was presumed to have been divided along with the corpus callosum. The massa intermedia was also divided where it was seen to be present (Bogen and Vogel, 1962; Bogen, Fisher and Vogel, 1965). Brief details about the individual patients are presented below. Full case reports have been published (Bogen *et al.*, 1965; Bogen, 1969; Sperry *et al.*, 1969) and a recent study of the neurological status of the patients is available (Bogen and Vogel, 1976).

L.B. was born in May 1952 and his first seizure occurred at the age of three years. Subsequently seizures became more severe and appeared more frequently and at operation in April 1965 all interhemispheric commissures were sectioned. He spoke readily on the first post-operative day and his recovery was rapid and uneventful. There were no radiological or other neurological signs of localized brain damage up to the time of his operation. He is right-handed.

N.G. is a 45-year-old housewife. Her seizures began at the age of 18 years and she showed radiological evidence of a calcified lesion one centimetre in diameter beneath the right cortex and EEG signs of an abnormality in the temporal lobe of the left hemisphere. The operation, performed in September, 1963, included section of the mass intermedia. Intelligible speech was uttered on the second post-operative day and recovery was uneventful. She is right-handed.

These two patients, L.B. and N.G. are presumed to present most clearly the syndrome of hemispheric disconnection because of their smooth recovery following operation and because extracallosal damage seemed to be minimal (Gazzaniga, Bogen and Sperry, 1967; Sperry *et al.*, 1969).

N.W. participated in some of the tests, as described below. She was born in May 1930 and her seizures began at the age of 3 years. She underwent commissurotomy in December, 1966. Prior to the operation there were EEG signs of diffuse disorganization without localization. At the time of testing there was some dyspraxia for the left upper limb to verbal commands.

Testing Procedures

In the major test the subjects performed a weight-matching task in which weights were lifted by simultaneously flexing the distal joint of each thumb. This movement is carried out by flexor pollicis longus. Details of the apparatus used and matching task have already been published (Gandevia and McCloskey, 1977*b*). In brief flexion of the distal joint of the thumb depressed one side of a see-saw device to lift the weights, which were hung in light buckets at the other end. The buckets were out of sight of the subjects. Subjects lifted a reference weight of 1000 g with one (reference) thumb and matched it with a variable weight, similarly lifted, by the other (matching) thumb. When the variable weight, which had been adjusted according to the subjects' instructions, equalled the reference weight then the chosen weight represented the perceived heaviness of the reference weight. When the left thumb lifted the reference weight the subjects verbally instructed the experimenter to increase or decrease the weight lifted by the right thumb until the subjects said they were the same. When the right thumb lifted the reference weight the subjects, after lifting the weights, signalled with their left index finger or thumb to the experimenter that weight needed to be added or removed on the left or that the weights lifted by both thumbs were apparently equal. Estimates were made as controls and were repeated when the long flexor of the thumb on the reference side was weakened by fatigue. Fatigue was produced by having the subject lift isometrically 2·5 kg until it could no longer be supported. A sphygmomanometer cuff, positioned around the upper arm, was then inflated above systolic pressure before the contraction was relaxed. This maintained the muscle in a weakened state (Merton, 1954). After about thirty seconds the subject made two estimates of the heaviness of the 1000 g reference weight. The cuff was then released and after two to four minutes two control estimates were made. This sequence was repeated five times with first the left then with the right side lifting the reference weight.

In a second set of experiments subjects lifted a 1000 g reference weight by flexing the elbow. Weights which were contained in buckets were attached over pulleys to padded bands around the subject's wrists. The buckets could not be seen by the subject. On alternate estimates the subject firmly grasped between fingers and thumb a piece of wide rubber tubing which was strapped into the (reference) hand. This method of lifting weights with the flexors of the elbow while grasping with the hand has been previously described in detail (Gandevia and McCloskey, 1976). L.B. made 15 and N.G. made 10 pairs of control estimates and estimates during grasping on the reference side. As in the fatigue experiments the left and then the right side lifted the reference weight and the same techniques for signalling the changes required by the subject on the matching side were used.

In another set of experiments the 'size-weight illusion' (*see* Charpentier, 1891) was examined. One wide beaker (100 mm diameter; 250 g) and four narrow beakers (12 mm diameter; 100, 150, 200 and 250 g) were used Beakers, grasped between the thumb and the index and middle fingers, were freely lifted. Initially subjects were required to align the beakers in order of either increasing or decreasing apparent weight. Alignment was made using just the left hand or just the right hand. It was repeated when the left hand lifted the wide beaker while the right lifted the narrow ones and then when the right lifted the wide beaker while the left lifted the narrow ones. In a more stringent test the subject was blindfolded and the weights were grasped and lifted from the table only by abduction (radial deviation) of the wrist. The subject lifted the wide beaker in one hand and selected a narrow beaker lifted by the other hand which was of apparently equal weight. Ten estimations were made when the wide beaker was lifted in the left hand and then in the right hand. The subject was led to believe that the weight in the large beaker was altered between trials.

In all matching tasks described above subjects were required to use the signalling system (speech, finger movement, or manual selection) devised for each test. Head or neck movements and speech at inappropriate times were not permitted

RESULTS

Perceived Heaviness during Fatigue

The two subjects N.G. and L.B. performed in the same way as normal subjects when the muscle which lifted a weight was fatigued. Perceived heaviness during fatigue, as judged by the matching weight chosen on the unfatigued side, increased. Results are shown in Table 1. The mean and scatter of the control estimates do not appear to differ from those of normal subjects (Gandevia and McCloskey, 1977*b*, *see* their fig. 5). In both subjects the perceived heaviness was significantly increased above the control levels when the lifting muscle was fatigued. Fatigue was produced first on the left side (as described under Methods) and both subjects when asked to

TABLE 1. CHANGES IN PERCEIVED HEAVINESS OF A 1000 G REFERENCE WEIGHT LIFTED BY FLEXING THE THUMB DURING FATIGUE. MEAN ± SEM FOR 10 ESTIMATES

	Left reference		*Right reference*	
	Control	*Fatigue*	*Control*	*Fatigue*
L.B.	1260±28	1570±45	845±32	1300±45
	$P < 0{\cdot}001$		$P < 0{\cdot}001$	
N.G.	890±43	1230±50	1100±49	1490±38
	$P < 0{\cdot}001$		$P < 0{\cdot}001$	

describe the feelings on the left during fatigue mentioned that the object they were lifting felt heavy. One subject, L.B., described an increase in apparent heaviness as the fatigue of the long flexor of the thumb progressed. This suggests that the left hemisphere may have been aware of the magnitude of the motor command being delivered by the right.

Perceived Heaviness during Grasping

In normal subjects the perceived heaviness of a reference weight lifted by flexing the elbow is usually reduced when the hand is also grasping (Gandevia and McCloskey, 1976). In subject L.B. there was a significant reduction in the perceived heaviness when either the left or right side lifted the reference weight. In N.G. there was a significant reduction in perceived heaviness when the reference weight was lifted on the right but no significant change when it was lifted on the left.

Size-weight Illusion

The larger of two objects having equal weight is usually judged to be lighter—this is the size-weight illusion (Charpentier, 1891; Woodworth, 1940; McCloskey, 1974). Four narrow beakers (100, 150, 200, 250 g: 12 mm wide) and one wide beaker (250 g: 100 mm wide) were used to see, first, whether each hemisphere individually experiences the illusion, and, secondly, whether the illusion is present when one hand lifts a wide beaker and the other lifts a narrow beaker.

When using one hand or both hands to place the five beakers in order of increasing or decreasing weight L.B. placed the wide beaker (250 g) after the narrow 100 g but before the narrow 200 g beaker. N.G., when using one or both hands, placed the wide beaker between the narrow 100 g and narrow 200 g beaker in 18 of 20 trials. Once the wide beaker was placed as if lighter than the narrow 100 g beaker and once it was placed between the narrow 200 g and the narrow 250 g beaker. Aside from positioning the wide beaker as if it was apparently lighter than the narrow 250 g one, the narrow beakers were usually aligned accurately. In 20 trials L.B. made one and N.G. four errors by misplacing one of the narrow beakers when the beakers were arranged in order of apparent weight.

In both subjects, when the perceived heaviness of the wide beaker was determined using a matching task, the wide beaker was again judged to be light, as shown by the weight of the narrow beaker lifted on the other side to match. Results are shown in Table 2.

TABLE 2. PERCEIVED HEAVINESS OF A WIDE 250 G BEAKER, LIFTED BETWEEN THUMB AND FINGERS, AS JUDGED BY THE WEIGHT OF A NARROW BEAKER LIFTED ON THE OTHER SIDE TO MATCH. MEAN ± SEM FOR 10 ESTIMATES

	Left reference	*Right reference*
L.B.	105±5	140±10
N.G.	120±8	155± 5

Results from N.W.

Although N.W. showed some dypraxia for the left upper limb she participated in two of the tests. The perceived heaviness of a 500 g reference weight lifted by flexing the distal joint of the left thumb was increased significantly when the long flexor of the thumb on the left was fatigued. (Fatigue was produced by a period of sustained weight-bearing, unaccompanied by inflation of the sphygmomanometer cuff, as used for L.B. and N.G.). When matching the heaviness of the wide beaker (250 g) lifted on one side with that of the narrow ones lifted on the other side she chose an average 160 ± 21 g when lifting the wide one on the right and an average 125 ± 15 g when lifting the wide one on the left (mean ± SEM for 10 estimates).

DISCUSSION

These results suggest that even in the absence of the neocortical commissures subjects rely on signals related to the voluntary motor command or effort rather than signals of achieved muscular tension in their judgement of weight. Although signals related to intramuscular tension were available, many of which have some access to both hemispheres, subjects preferred to neglect them in favour of signals related to the size of the outgoing motor command to the motoneurons when judging heaviness. In this respect they perform as accurately and in the same way in their judgements as normal subjects who have been tested under similar conditions (McCloskey *et al.*, 1974; Gandevia and McCloskey, 1977*a*, *b*, *c*).

One interpretation of the fatigue experiments, in which subjects matched the increased centrally-generated effort to lift on the weakened side with an increased effort (which lifted a larger weight) on the other side, is that information about the magnitude of the motor command reached both hemispheres. Insufficient is known about the centrally-generated effort or voluntary motor command which signals heaviness to discuss in detail the anatomical implications of this interpretation. The results, however, permit the following speculation. Signals of outgoing motor activity which the sensorium uses to estimate weight cross into the opposite hemisphere at levels beneath the neocortical commissures. These signals of effort not dependent upon the corpus callosum to reach the other hemisphere may thus be 'low level' outputs of the motor system.

Another explanation for the findings presented here is that comparisons of weight were made within one hemisphere using contralateral and ipsilateral motor paths to determine the relative motor commands to the left and right side. For several reasons this possibility is considered unlikely. First, ipsilateral motor outflow to the distal musculature is less than that for proximal and axial musculature (Liu and Chambers, 1964; Gazzaniga, 1970; Brinkman and Kuypers, 1973; Glees, 1975; Zülch, 1975; cf. Zaidel and Sperry, 1977). Difficulty might be expected in comparing the motor commands delivered from the one hemisphere to both sides, when the movements are made simultaneously. Activity of the contralateral motor system 'suppresses' that in the ipsilateral motor system (Sperry *et al.*, 1969).

When the reference weight was lifted on the right and changes in weight were signalled by movement of digits on the left, on rare occasions both N.G. and L.B. verbally requested an alteration in weight. These spoken requests were consistent with the matching weights chosen when signalling only with digits on the left. Finally, and perhaps most importantly, the subjects showed an internal consistency in the selection of control estimates whichever side lifted the reference weight. Thus if the subject matched the 1000 g reference weight on the left with, say, 1200 g on the right, then the 1000 g reference weight on the right was matched with a smaller weight, say, 800 g on the left. If a different hemisphere were responsible for judgement of weight when different sides lifted the reference weight it would be surprising if both showed the same deviation in the internal calibration for weight.

A third possible explanation is that afferents from muscle spindles in the contracting muscles provided the signals used by the split-brain subjects for weight estimation (cf. McCloskey *et al.*, 1974). These afferents discharge during voluntary movements (*see* Vallbo, 1971, 1974) and their discharges reach both hemispheres (McCloskey, 1973). In these subjects, however, one hemisphere usually attends to only the contralateral afferent input when stimuli are presented simultaneously to both sides (Sperry *et al.*, 1969).

Ferrier (1876) suggested that sensation of the effort put into a muscular contraction is usually due to perception of the activity of other muscles (for example, respiratory muscles) which are called into graded activity at the time of the effort. It is thus possible that the results presented here are due to perception of afferent information generated in a remote muscle group which has access to both hemispheres. This is analogous to some cross-cuing strategies devised by split-brain animals and human subjects to present information to both hemispheres (Mark and Sperry, 1968; Gazzaniga, 1966, 1970; Bogen and Vogel, 1976). Perception of afferent discharges from a remote muscle group as a signal of effort does not seem an attractive explanation for the findings presented here because the lifting contractions were produced simultaneously on the two sides. Thus while afferent information would be generated by partial fixation of the ribs (to use Ferrier's example), such information is unlikely to be able to signal separately the motor commands (or effort) being simultaneously delivered to both the lifting muscles on the left *and* to those on the right.

Both N.G. (on one side) and L.B. (on both sides) performed in the same way as most normal subjects when estimating the heaviness of a weight lifted by flexing the elbow while the sensory input arising in the hand was enhanced by grasping. Perceived heaviness is reduced (Gandevia and McCloskey, 1976). It has been argued that the increased sensory input from the hand during a grasp assists or facilitates the contraction of the ipsilateral flexors of the elbow. This reduces the voluntary motor command required to lift the same weight and thus reduces the apparent heaviness of the weight (Gandevia and McCloskey, 1976, 1977*b*). The apparently normal performance of the commissurotomy patients in this task is consistent with the explanation that each hemisphere was 'aware' of the magnitude of the motor commands delivered to the relevant motoneurons on the left and right sides.

Perhaps the most surprising result is that the size-weight illusion was preserved as tested with an interhemispheric matching task when lifting movements were limited and vision was excluded. The conventional explanation for the illusion is that on the basis of experience larger objects are expected to be heavy and smaller ones to be light. Information about the size or width of the object is presumably signalled by kinæsthetic cues and departure of 'real' from 'expected' weight provides the 'illusion' (Sherrington, 1900; Woodworth, 1940). It is not easy to speculate as to how the level of 'expectation' of weight might be available to both hemispheres. However, if, as the results suggest, each hemisphere has experience of the illusion, and if information about the motor command is transmitted to both hemispheres, then if sufficient information about the width (size) of the lifted object reaches the ipsilateral hemisphere, comparisons between real and expected weight may be made within each hemisphere separately. It is not necessary to postulate that a hypothetical level of 'expectation' is transferred between the hemispheres; sufficient information for either hemisphere to deduce the expected weight may be available.

While the most likely explanation for the findings in the split-brain subjects is that corollary motor discharges or discharges related to outgoing motor commands reach both hemispheres, use of this information does not confer as acute an ability for bimanual co-ordination as exists in normal subjects. Some impairment of bimanual co-ordination has recently been revealed in studies of the split-brain subjects, especially in tasks in which there was a specific requirement for speed or alternating bilateral movements (Preilowski, 1972; Zaidel and Sperry, 1977; *see also* Kreuter, Kinsbourne and Trevarthen, 1972). Bilateral distribution of the motor command, however, may be sufficient to explain the seemingly normal behaviour of the split-brain patients in the simple weight-matching tasks used here.

SUMMARY

The sensation of heaviness was examined in three subjects who had undergone surgical division of the neocortical commissures. Subjects estimated the heaviness of weights lifted on one side by matching them with weights, simultaneously lifted, on the other side. In one test weights were lifted by flexing the distal joint of the thumb before and after fatigue of the lifting muscle. There was an increase in the perceived heaviness of a weight lifted by the weakened muscle, as judged by the larger weight chosen on the unfatigued side to match it. In this and another test, both of which involved alteration of the central motor command or effort required to lift a weight, the split-brain subjects performed in a qualitatively similar way to normal subjects.

The subjects also performed in an apparently normal way in tests requiring interhemispheric transfer of the size-weight illusion.

As the perceived heaviness of a lifted object, under the conditions used, depends on sensing the effort or voluntary motor command put into the lifting contraction and not on afferent signals of cutaneous pressure or intramuscular tension (*see* McCloskey *et al.*, 1974) these findings suggest that information about the magnitude of the voluntary motor command may be accessible to both hemispheres.

ACKNOWLEDGEMENTS

These experiments were supported by a grant (MH 03372) from the National Institute of Health of the United States Public Health Service to Professor R. W. Sperry, and by the National Health and Medical Research Council of Australia. I thank Professor Sperry for providing the subjects, the laboratory facilities and helpful discussion. I thank Dr. Ian McCloskey (University of New South Wales) for his proposal of these experiments and for criticism of the manuscript.

REFERENCES

AKELAITIS, A. J. (1944) A study of gnosis, praxis and language following section of the corpus callosum and anterior commissure. *Journal of Neurosurgery*, **1**, 94–102.

BOGEN, J. E. (1969) The other side of the brain. I. Dysgraphia and dyscopia following cerebral commissurotomy. *Bulletin of the Los Angeles Neurological Society*, **34**, 73–105.

—— FISHER, E. D. and VOGEL, P. J. (1965) Cerebral commissurotomy: A second case report. *Journal of the American Medical Association*, **194**, 1328–1329.

—— and VOGEL, P. J. (1962) Cerebral commissurotomy in man. Preliminary case report. *Bulletin of the Los Angeles Neurological Society*, **27**, 169–172.

—— —— (1976) Neurological status in the long term following complete cerebral commissurotomy. In: *Les Syndromes de Disconnexion Calleuse chez l'Homme*. Edited by F. Michel and B. Schott. Lyon: Hôpital Neurologique, pp. 227–251.

BRINKMAN, J. and KUYPERS, H. G. J. M. (1973) Cerebral control of contralateral and ipsilateral arm, hand and finger movements in the split-brain rhesus monkey. *Brain*, **96**, 653–674.

CHARPENTIER, A. (1891) Analyse expérimentale de quelques éléments de la sensation de poids. *Archives de physiologie normale et pathalogique*, **3**, 121–135. Cited by R. Granit (1972). Constant errors in the execution and appreciation of movement. *Brain*, **95**, 649–660.

FERRIER, D. (1876) *The Functions of the Brain*. 1st Edition. London: Smith Elder, pp. 223–224.

FULTON, J. F. (1943) *Physiology of the Nervous System*. 2nd Edition: Oxford University Press, p. 265.

GANDEVIA, S. C. and MCCLOSKEY, D. I. (1976) Perceived heaviness of lifted objects and effects of sensory inputs from related, non-lifting parts. *Brain Research, Amsterdam*, **109**, 399–401.

—— —— (1977*a*) Sensations of heaviness. *Brain*, **100**, 345–354.

—— —— (1977*b*) Effects of related sensory inputs on motor performances in man studied through changes in perceived heaviness. *Journal of Physiology, London*, **272**, 653–672.

—— —— (1977*c*) Changes in motor commands, as shown by changes in perceived heaviness, during partial curarization and peripheral anaesthesia in man. *Journal of Physiology, London*, **272**, 673–689.

GAZZANIGA, M. S. (1966) Interhemispheric cuing systems remaining after section of neocortical commissures in monkeys. *Experimental Neurology*, **16**, 28-35.

—— (1970) *The Bisected Brain*. New York: Appleton Century Crofts, pp. 21, 29, 51.

—— BOGEN, J. E. and SPERRY, R. W. (1967) Dyspraxia following division of the cerebral commissures. *Archives of Neurology*, **16**, 606-612.

GLEES, P. (1975) Contra- and ipsilateral motor and sensory representation in the cerebral cortex of monkey and man. In: *Cerebral Localization*. Edited by K. J. Zülch, O. Creutzfeldt and G. C. Galbraith, Berlin: Springer-Verlag, pp. 48-61.

HOLMES, G. (1917) The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain*, **40**, 461-535.

INNOCENTI, G. M., MANZONI, T. and SPIDALIERI, G. (1972) Cutaneous receptive fields of single fibers of the corpus callosum. *Brain Research, Amsterdam*, **40**, 507-512.

—— —— —— (1974) Patterns of somesthetic messages transferred through the corpus callosum. *Experimental Brain Research*, **19**, 447-466.

JONES, E. G., BURTON, H. and PORTER, R. (1975) Commissural and cortico-cortical 'columns' in the somatic sensory cortex of primates. *Science*, **190**, 572-574.

—— and POWELL, T. P. S. (1969) Connexions of the somatic sensory cortex of the rhesus monkey. II. Contralateral cortical connexions. *Brain*, **92**, 717-730.

KREUTER, C., KINSBOURNE, M. and TREVARTHEN, C. (1972) Are disconnected cerebral hemispheres independent channels? A preliminary study of the effect of unilateral loading on bilateral finger tapping. *Neuropsychologia*, **10**, 453-461.

LEVY, J. and SPERRY, R. W. (1970) Crossed temperature discrimination following section of forebrain neocortical commissures. *Cortex*, **6**, 349-361.

LIU, C. N. and CHAMBERS, W. W. (1964) An experimental study of the corticospinal system in the monkey (*Macaca mulatta*). *Journal of Comparative Neurology*, **123**, 257-283.

McCLOSKEY, D. I. (1973) Position sense after surgical disconnexion of the cerebral hemispheres in man. *Brain*, **96**, 269-276.

—— (1974) Muscular and cutaneous mechanisms in the estimation of weights of grasped objects. *Neuropsychologia*, **12**, 513-520.

—— EBELING, P. and GOODWIN, G. M. (1974) Estimation of weights and tensions and apparent involvement of a 'sense of effort'. *Experimental Neurology*, **42**, 220-232.

MARK, R. F. and SPERRY, R. W. (1968) Bimanual coordination in monkeys. *Experimental Neurology*, **21**, 92-104.

MERTON, P. A. (1954) Voluntary strength and fatigue. *Journal of Physiology, London*, **123**, 553-564.

NEBES, R. D. and SPERRY, R. W. (1971) Hemispheric deconnection syndrome with cerebral birth injury in the dominant arm area. *Neuropsychologia*, **9**, 247-259.

PENFIELD, W. and RASMUSSEN, T. (1950) *The Cerebral Cortex of Man*. New York: Macmillan, p. 184.

PREILOWSKI, B. F. B. (1972) Possible contribution of the anterior forebrain commissures to bilateral motor co-ordination. *Neuropsychologia*, **10**, 267-277.

ROLAND, P. E. and LADEGAARD-PEDERSEN, H. (1977) A quantitative analysis of sensations of tension and of kinæsthesia in man. *Brain*, **100**, 671-692.

SHANKS, M. F., ROCKEL, A. J. and POWELL, T. P. S. (1975) The commissural fibre connections of the primary somatic sensory cortex. *Brain Research, Amsterdam*, **98**, 166–171.

SHERRINGTON, C. S. (1900) The muscular sense. In: *Textbook of Physiology*. Edited by E. A. Schafer. Edinburgh: Pentland, Vol. 2, pp. 1002–1025.

SPERRY, R. W. (1966) Brain bisection and mechanisms of consciousness. In: *Brain and Conscious Experience*. Edited by J. C. Eccles. Heidelberg: Springer-Verlag, pp. 298–313.

—— (1974) Lateral specialization in the surgically separated hemispheres. In: *The Neuroscience Third Study Program*. Edited by F. O. Schmitt and F. G. Worden. Massachusetts: MIT Press, pp. 5–19.

—— GAZZANIGA, M. S. and BOGEN, J. E. (1969) Interhemispheric relationships: the neocortical commissures; syndromes of hemispheric disconnection. In: *Handbook of Clinical Neurology*. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, Vol. 4, pp. 273–290.

VALLBO, A. B. (1971) Muscle spindle response at the onset of isometric voluntary contractions in man. Time difference between fusimotor and skeletomotor effects. *Journal of Physiology, London*, **218**, 405–431.

—— (1974) Human muscle spindle discharge during isometric voluntary contractions. Amplitude relations between spindle frequency and torque. *Acta Physiologica Scandinavica*, **90**, 319–336.

WHITE, R. J., SCHREINER, L. H., HUGHES, R. A., MACCARTY, C. S. and GRINDLAY, J. H. (1959) Physiologic consequences of total hemispherectomy in the monkey. *Neurology, Minneapolis*, **9**, 149–159.

WOODWORTH, R. S. (1940) *Psychology*. 12th Edition. London: Methuen, p. 459.

ZAIDEL, D. and SPERRY, R. W. (1977) Some long-term motor effects of cerebral commissurotomy in man. *Neuropsychologia*, **15**, 193–204.

ZÜLCH, K. J. (1975) Pyramidal and parapyramidal motor systems in man. In: *Cerebral Localization*. Edited by K. J. Zülch, O. Creutzfeldt and G. C. Galbraith. Berlin: Springer-Verlag, pp. 32–47.

(*Received November 10, 1977*)

Brain (1978), **101**, 307-332

SOMATOSENSORY EPILEPSY

A REVIEW OF 127 CASES

by F. MAUGUIERE *and* J. COURJON

(*From the Service EEG de l'Hôpital Neurologique, 59 Boulevard Pinel 69003, Lyon, France*)

SINCE Jackson's first description of paræsthetic epileptiform seizures in 1863, most studies of somatosensory epilepsy have investigated the pathophysiological mechanisms and the localizing value of the somatosensory seizures. Penfield and the Montreal school have demonstrated that the paroxysmal somatic sensations which are characteristic of the patient's spontaneous seizures can be reproduced by electrical stimulation of those areas of the parietal cortex which are involved in the reception or integration of somæsthetic information, namely, the primary and secondary somatosensory areas (SI and SII) and the supplementary somatosensory area in the inner part of Brodmann's area 5 (Penfield and Gage, 1933; Penfield and Erickson, 1941; Penfield and Jasper, 1954). Since these early studies, the classification of somatosensory seizures has been based on clinical and pathophysiological data. Each type of seizure has been defined by its lateralization, the nature and position of the paroxysmal sensations, and the site of origin and spread of the cortical ictal discharge (Gastaut, 1954, 1969; Gastaut and Broughton, 1972).

Thus, unilateral paræsthetic seizures, with or without a progression of somatosensory symptoms in a 'Jacksonian march', are considered to be the clinical expression of a discharge localized in the contralateral area SI. It is commonly assumed that bilateral paræsthetic seizures are due to a discharge affecting either SII or the supplementary sensory area (Penfield and Rasmussen, 1950). Complex somatosensory seizures with paroxysmal disturbances of somatognosia are generally correlated with ictal discharges situated in the posterior parietal areas of the minor hemisphere. Stereo-electroencephalographic recordings of somatosensory seizures have confirmed all these electroclinical correlations in a small number of cases (Bancaud and Talairach, 1965; Trottier, 1972; Bancaud, Talairach, Geier and Scarabin, 1973).

Statistical study of the clinical and ætiological aspects of somatosensory epilepsy has been performed on only two previous occasions (Penfield and Kristiansen, 1951; Lende and Popp, 1976), and only one detailed clinical and anatomical study of sensory fits of traumatic origin has been published (Russell and Whitty, 1953). This may be explained by the very low incidence of somatosensory epilepsy, which represented only 1·42 per cent of the 8,938 epileptic patients followed over a ten-year period (1965–1975) in our EEG department. Our purpose is, first, to give a clinical description of the seizure patterns observed in a population of 127 patients suffering from somatosensory epilepsy and secondly, to discover the respective frequencies of the different ætiologies.

MATERIAL AND METHODS

Selection of Patients

Of 127 patients with somatosensory epilepsy seen in the University Hospital of Lyon between 1965 and 1975, 82 had been admitted to neurological wards and 45 to neurosurgical wards. These patients were selected from a population of 8938 epileptic patients (more than 3 years old) who had been admitted to the same hospital during the same period.

Only patients with complete clinical details (*see* Table 1) were investigated. Only cases in which paræsthesiæ, pain or somatognostic disturbances were clearly the prevalent ictal symptoms were selected.

TABLE 1. INFORMATION REQUIRED FOR SELECTION OF PATIENTS

1. Date of birth and sex
2. Date of onset of somatosensory seizures
3. Nature of ictal somæsthetic symptoms
4. Side of seizures
5. Initial localization and maximal spread of somæsthetic ictal symptoms
6. Nature of possible non-somæsthetic ictal symptoms
7. Frequency of secondary generalized somatosensory seizures
8. Nature of all other epileptic disorders (associated non-somatosensory seizures)
9. Date and results of first neurological examination
10. Number and dates of EEG recordings
11. Date and order of first abnormal EEG
12. Lateralization, localization and type of EEG abnormalities
13. Dates, nature and results of all isotopic or neuroradiological investigations
14. Neurosurgeon's observations in all operated cases
15. Histological study of lesion in all operated cases

A routine electroencephalographic (EEG) recording with hyperventilation and intermittent photic stimulation was performed in all patients. Two or more EEGs (maximum 15) were carried out in 67 patients. Bemegride was intravenously injected under EEG control in 37 patients in order to induce an electroclinical seizure (maximal dose 3 mg per kg body weight). EEGs were recorded with the usual international 21 electrode system on an 18 channel recorder, both monopolar and bipolar derivations being used. Only EEG recordings obtained before any neurosurgical treatment were analysed in the present study.

Cerebral angiographic investigations or radio-isotope scanning were carried out in 107 patients. 6 patients had one or more isotope scans without carotid angiography, 27 patients had carotid angiograms only and 74 patients had both. Pneumoencephalography was undertaken in 14 patients. In the group subjected to neurosurgery (76 cases, 59·8 per cent), the nature of the causal lesion was always verified histologically. In 30 out of 51 patients in whom surgery was not performed the ætiological diagnosis was obvious from the previous case history or neuroradiological investigations. In the remaining cases the origin of the somatosensory epilepsy remained unknown, in spite of isotopic and neuroradiological investigations. All patients belonging to this latter group have been followed for more than one year (mean fifteen months) in a neurology department.

Patients

Among the 127 selected patients, 45 were females (35·4 per cent) and 82 were males (64·6 per cent). The mean age of onset of somatosensory epilepsy was 37·3 years (variance = 222, standard deviation (SD) = 15·6); the age distribution of onset is represented in fig. 1. Neither the mean age of onset nor the sex distribution were found to differ statistically between patients admitted to neurological wards and those admitted to neurosurgical wards (t = 1·24 for mean age of onset, $\chi^2 = 0{\cdot}00$ for sex distribution). The frequency of the somatosensory seizures was known with sufficient accuracy in 111 patients (*see* fig. 2). Evaluation of the seizure frequency was made only in the pre-operative period; 28 patients were classified in a 'single seizure' category either because they were subjected to operation shortly after the onset of symptoms or because they experienced only a single somatosensory epileptic episode in the course of their illness. In 36 patients (28·3 per cent) secondary generalized seizures were invariably observed. 35 patients (27·4 per cent) experienced at least one secondary generalized seizure with somatosensory onset. Non-somatosensory seizures occurred in 37 patients (29 per cent), details of ictal patterns observed in these patients are given in fig. 3. In 17 cases several types of non-somatosensory seizures could be observed in a single patient. On initial clinical examination permanent interictal neurological impairment was found in 67 patients (*see* fig. 4). The interval between the first somatosensory seizure and initial clinical examination by a neurologist was less than three months in 62 patients; three months to one year in 24 patients; more than one year in 41 patients.

Interictal EEG abnormalities were present in 91 patients (71·5 per cent). In 76 cases (60 per cent), these abnormalities were observed in the first recording. In 87 patients with abnormal interictal EEGs pathological tracings were recorded only from the hemisphere contralateral to the clinical seizures; in the 4 remaining patients the EEG abnormalities were bilateral, diffuse and roughly symmetrical. The topography of the lateralized EEG abnormalities is summarized in fig. 5. Forty-nine patients showed focal EEG disturbances in only one area. Two or more of these areas were affected in all other cases. The distribution of EEG abnormalities found in those patients with abnormal routine EEG was as follows: intermittent slow-waves, theta or delta (55 cases); permanent slow delta waves (34 cases); spikes-and-waves (21 cases). In 17 patients two of these pathological patterns could be observed, the most frequent association being spikes and intermittent slow-waves.

The exact sites of the lesions were determined in 92 cases, in 76 by direct observation during operation, and in 26 by neuroradiological investigations. Diffuse lesions involving both hemispheres were exceptional (5 cases); usually only the hemisphere contralateral to the clinically affected side of the body was damaged (87 cases). The localization of the lesion is represented in fig. 6; all lesions situated either in primary sensory area SI or in somatomotor area 4 are classified as 'central'. Lesions were highly focalized in only 38 patients (fig. 7) of whom the central area and the posterior parietal areas could be considered as undamaged in 17 cases (45 per cent), their lesion being either temporal or anterior frontal. In the other 54 patients at least two of the hemispheric areas outlined in fig. 6 were damaged.

Data Processing and Statistics

For each patient all the criteria pertaining to the description of the seizures, the clinical course of the illness, the dates and the results of EEG and isotopic and radiological investigations were card-indexed with 387 possible entries. Special attention was paid to the detailed description of the ictal symptoms. An Iris 55 computer was used for classification of data, counting operations, and calculation of Student t-test and χ^2 test. The value of t and χ^2 coefficients is recorded only when probability of error P is less than 0·05.

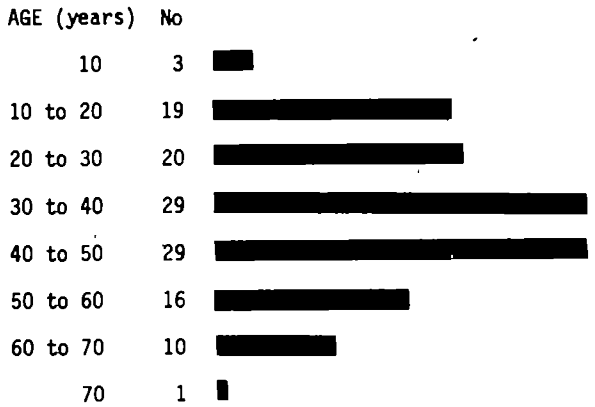


FIG. 1. Age of onset.

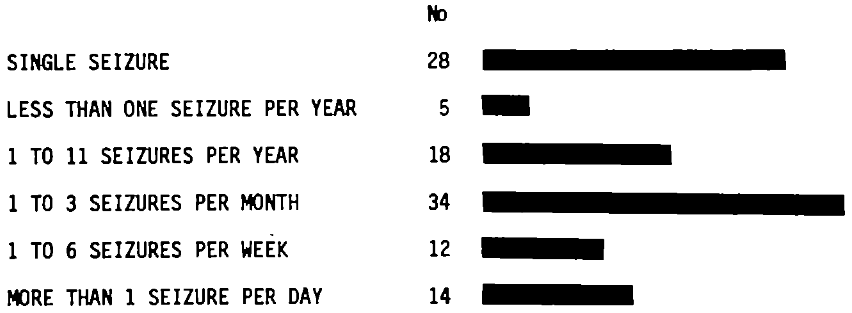


FIG. 2. Frequency of somatosensory seizures.

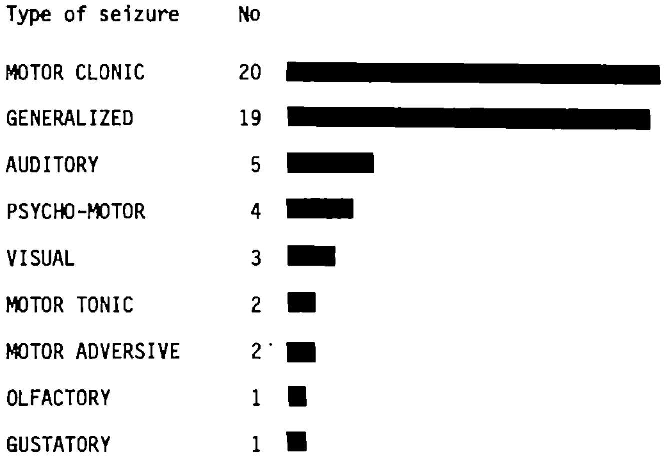


FIG 3. Associated non-somatosensory seizures in 37 patients.

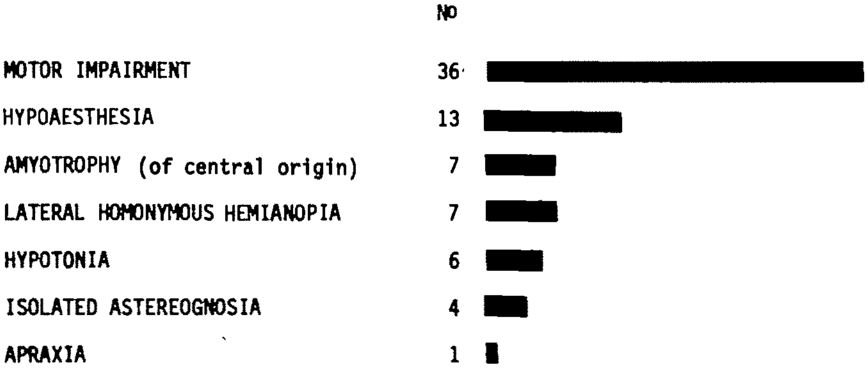


FIG. 4. Unilateral interictal neurological impairment at first examination in 67 patients

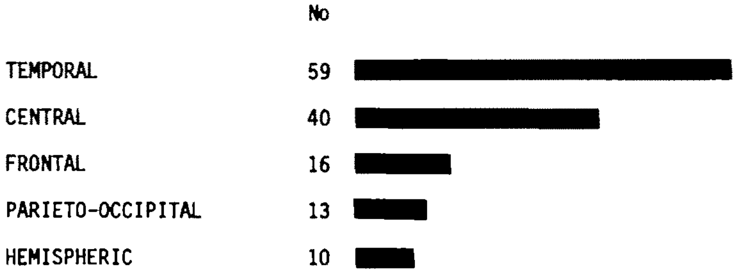


FIG. 5. Localization of unilateral EEG abnormalities in 87 patients

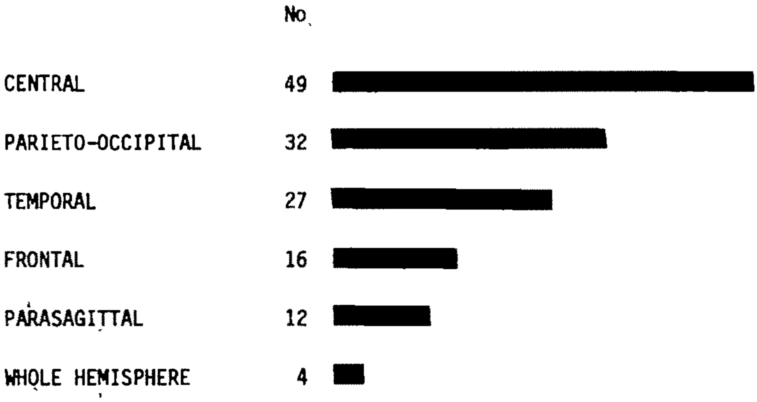


FIG 6. Localization of unilateral lesions in 92 patients: frequency of cases with damage to one at least of these regions.

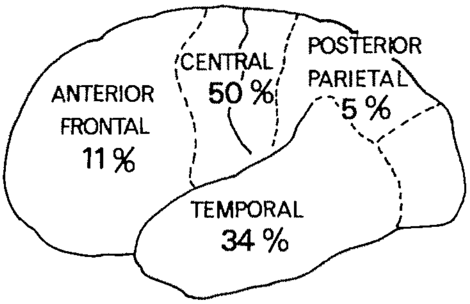


FIG. 7. Topographical distribution of focal lesions in 38 patients (*see* text).

RESULTS

Frequency of Somatosensory Epilepsy

In our 8938 epileptic patients somatosensory seizures and Jacksonian tonic-clonic fits were found to be the less frequent types of partial seizures, as shown in fig. 8. Only the neurovegetative and visceral seizures (not represented in fig. 8) with a frequency of 0·59 per cent were less common than somatosensory seizures in our group of patients.

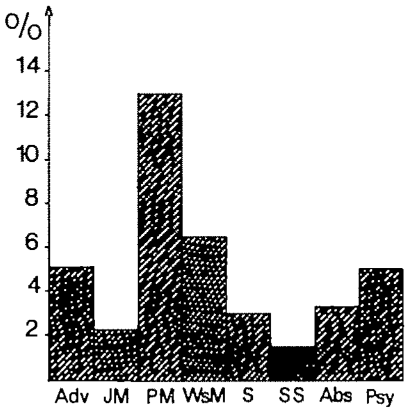


FIG. 8. Frequencies (per cent) of different types of partial seizures in a group of 8938 epileptic patients (more than three years old).

Adv = adversive seizures	461 cases	5·16%
JM = 'Jacksonian' motor seizures	199 cases	2·23%
PM = partial tonic or clonic motor seizures	1158 cases	12·93%
WsM = whole side motor seizures	582 cases	6·51%
S = sensory seizures (auditory, visual, gustatory, olfactory)	262 cases	2 93%
SS = somatosensory seizures	127 cases	1·42%
Abs = absences of short duration with automatism	293 cases	3 28%
Psy = psychomotor seizures	449 cases	5·02%

Clinical analysis of Ictal Patterns

Nature of ictal symptoms. Somatosensory symptoms (Table 2). Elementary paræsthesiæ (that is, pricking or tingling sensations, pins and needles) were the most frequent ictal symptoms; they were the only somæsthetic symptoms in 79 patients. Seizures which were only painful (2 cases) or 'somatognostic' (3 cases) were few. In 43 cases two or three of the symptoms listed in Table 2 were reported by the patients. Pure sensations of cold or heat were never experienced in isolation but were described as accompanied by pain by 6 patients, or associated with elementary paræsthesiæ in all other cases. Similarly, painful seizures, not including thermal sensations, were also usually paræsthetic. Eight patients who described their seizures as being painful had cramp-like sensations with tonic muscular spasm of the limb, subsequent to paræsthesiæ. In our series of 13 cases of paroxysmal somatognostic dysfunction 9 patients described a sensation of swelling of one of their hands or of their tongue (with associated paræsthesiæ in 6 cases and pain in one case). Two patients reported a sensation of shrinking of one of their upper limbs with associated paræsthesiæ. One patient described a paroxysmal left hemiasomatognosia, and one patient had brief sensations of levitation with left-sided paræsthesiæ.

TABLE 2. ICTAL SYMPTOMS

	No. of patients	*Per cent*
Paræsthesiæ	114	89·7
Pain	30	23·6
Sensation of warmth or cold	14	11·0
Somatognostic illusions	13	10·2

Non-somatosensory symptoms. In 75 cases (59 per cent) non-somæsthetic symptoms were reported by the patients or observed by the clinician during the seizures (fig. 9).

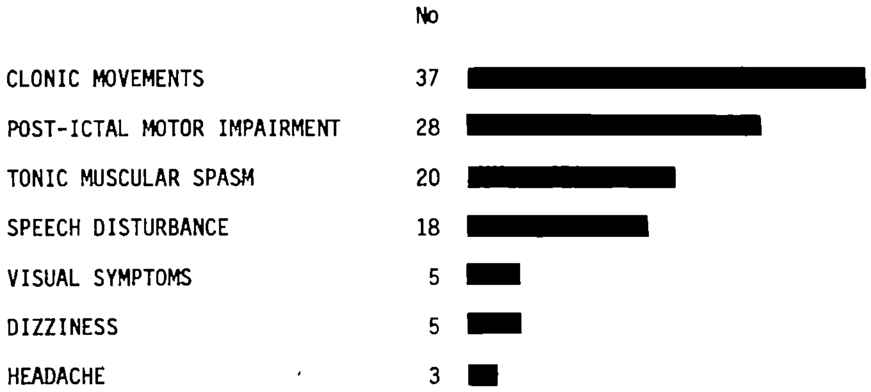


FIG. 9. Non-somatosensory ictal symptoms in 75 patients.

The high frequency of tonic or clonic motor phenomena is noteworthy. In this group of patients, 37 had paræsthesiæ with tonic-clonic Jacksonian seizures; in 12 others the paræsthesiæ of one limb were followed by postural change which could be either a tonic flexion of the forearm, with abduction of the shoulder and head rotation towards the elevated arm (9 cases) or extension and hyperpronation of the upper limb (3 cases). In one of the latter the hyperextension of the upper limb was associated with a retropulsion of the shoulder and contralateral head rotation. Post-ictal motor impairment usually occurred after Jacksonian sensorimotor seizures (16 cases); in 11 cases, however, the motor deficit was not preceded by any tonic or clonic phenomena. Post-ictal motor impairment was found to be statistically more frequent after seizures of upper limbs ($\chi^2 = 4{\cdot}06$, $P < 0{\cdot}05$).

In contrast, visual ictal symptoms were rare in our series and reported by 5 patients only (phosphenes in one visual hemifield, 2 cases; macropsia, one case; and formed visual hallucinations, 2 cases).

18 patients (14·2 per cent) described a transient disturbance of speech which occurred either before (9 cases) or after (9 cases) the somatosensory ictal symptoms. The clinical analysis of these speech disturbances is difficult in most cases. However, arrest of speech and transient dysarthria seemed to be the most frequent. All these patients were right-handed and experienced right-sided seizures.

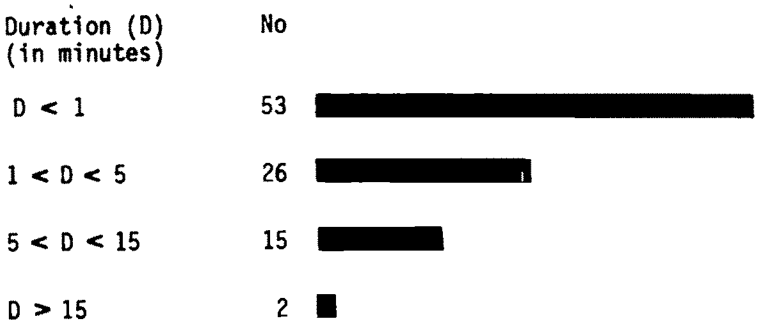


FIG. 10. Duration of ictal somatosensory symptoms in 96 patients

Duration of somatosensory symptoms. When questioned on the duration of the somatosensory ictal symptoms, 96 patients (75·6 per cent) were able to make an approximate estimate (fig. 10). It appeared that brevity was an almost constant characteristic. This was corroborated by study of our series of 21 seizures which occurred during EEG recording. Their mean duration was 120 seconds (max. = 480 s, min. = 20 s, SD = 99·3). No statistically significant correlation between the duration and the different types of ictal patterns has been found.

Localization of seizures. With one exception all patients had unilateral seizures, which were right-sided in 64 patients (50·4 per cent), and left-sided in 62 patients (48·8 per cent). The complex seizures with somatognostic disturbances were left-sided in 7, and right-sided in 6 of 13 patients, all of whom were right-handed. Only one patient described secondary spread of the paræsthesiæ to the opposite side: beginning in the right hand, the fit spread to the right side of the face, then to the left side of the face and eventually to the left hand at the end of the seizure.

The most frequent initial localization was the hand and the fingers (fig. 11). The large number of seizures beginning in the foot may be related to the frequency of parasagittal lesions, particularly meningiomas, in our series (*vide infra*).

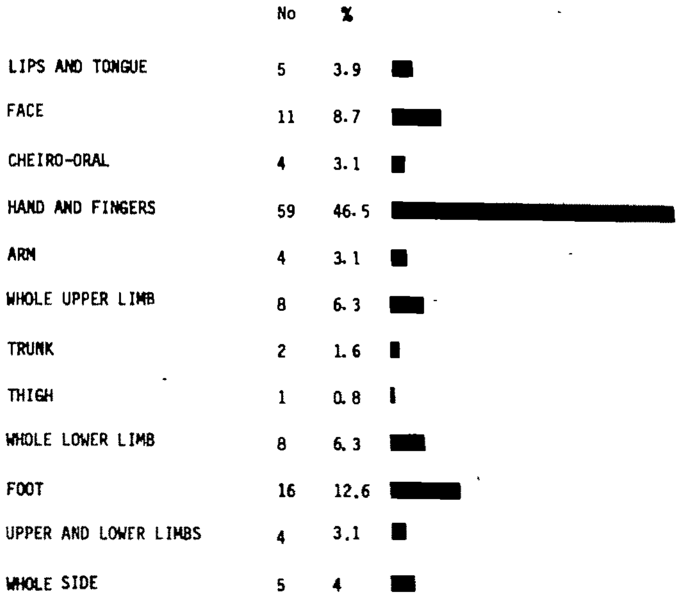


FIG. 11 Initial localization of ictal somatosensory symptoms in 127 patients.

In 88 cases (79 per cent) the somæsthetic symptoms spread during the seizure; 86 patients could give an accurate description of the maximal extent of their symptoms (fig. 12). In most cases (81) the mode of extension of the paræsthesiæ was compatible with a progressive cortical spread of the discharge along the primary sensory area SI. The extent of the paræsthesiæ beginning in fingers or hand was often limited to the upper limb or to the forearm (fig. 13). In attempting to correlate the extension and site of origin of the somæsthetic symptoms we found extension to one entire side of the body to be more frequent in the seizures beginning in the lower limb (71 per cent), than in those beginning in the upper limb or face (44 per cent). This difference is statistically significant ($\chi^2 = 11{\cdot}54$, $P < 0{\cdot}01$). No significant correlation was found between the secondary generalization of seizures and the site of origin or the maximal spread of the ictal somæsthetic symptoms. The secondary generalization of seizures was not correlated with the involvement of the face.

Localizing value of ictal symptoms. In the 92 patients in whom the lesion could be localized, the contralateral hemisphere was always damaged. Little of significance was found on investigating correlations between the characteristics of the seizures defined above (type, duration, localization of the somæsthetic symptoms), and the site of the lesions. Seizures beginning in the foot were found to be specifically related to parasagittal lesions ($\chi^2 = 13{\cdot}75$; $P < 0{\cdot}01$); burning sensations and painful paræsthesiæ were more frequent when the centroparietal region was undamaged (χ^2 with Yates correction $= 4{\cdot}08$, $P < 0{\cdot}05$ for burning sensations; $\chi^2 = 6{\cdot}7$, $P < 0{\cdot}01$ for painful paræsthesiæ). No statistically significant correlations have been found between the site of the lesions and any of the following parameters: somatognostic disturbance; initial localization (foot excepted) and maximal spread of ictal symptoms; seizure duration; presence of ictal motor symptoms; and frequency of secondary generalization. In the 13 patients with complex seizures the posterior parietal areas were undamaged in 9 cases.

Clinical ictal patterns. Of the various ictal patterns we have observed, somatosensory seizures might be classified into three main categories: purely somatosensory seizures (62 cases, 48·7 per cent), somatosensory and motor seizures (60 cases, 47·4 per cent), and visual-somæsthetic seizures (5 cases, 3·9 per cent). Nearly 80 per cent of the patients with purely somatosensory seizures had simple or elementary seizures (49 cases, 79·1 per cent). In the group of patients with somatosensory and motor seizures, the most frequent ictal pattern was transient paræsthesiæ followed by a Jacksonian tonic-clonic seizure (37 cases); in 12 cases the somæsthetic symptoms were associated with a tonic change of posture; in the 11 remaining cases, patients described paræsthesiæ accompanied by a transient motor impairment without tonic or clonic motor phenomena. The latter type of seizure could be interpreted either as somatomotor inhibitory seizures, or as seizures with paroxysmal motor neglect. However as patients often mistake paræsthetic sensations for transient motor impairment, the distinction between the two may be difficult. Such a classification is in some respects unsatisfactory as it ignores the complexity and variability of the associations we have observed.

Ictal EEG patterns. In 32 patients (25·2 per cent) at least one focal seizure has been recorded electroencephalographically. These seizures were spontaneous (5 cases) or induced by hyperventilation (16 cases), intravenous injection of Bemegride (10 cases), or intermittent photic stimulation (one case). In 6 patients the seizures were electrically silent. In 7 patients with both somatosensory and motor seizures, only an exclusively focal motor seizure could be recorded. Simultaneous EEG records were obtained during somatosensory seizures in 19 patients (Table 3). In this group, the ictal EEG abnormalities included sustained discharges of spikes (as in fig. 14) and rhythmic slow-waves, which began, in all cases, in the contralateral hemisphere. During the somatosensory seizures the EEG discharges were recorded in the central region in 14 patients and in the temporal

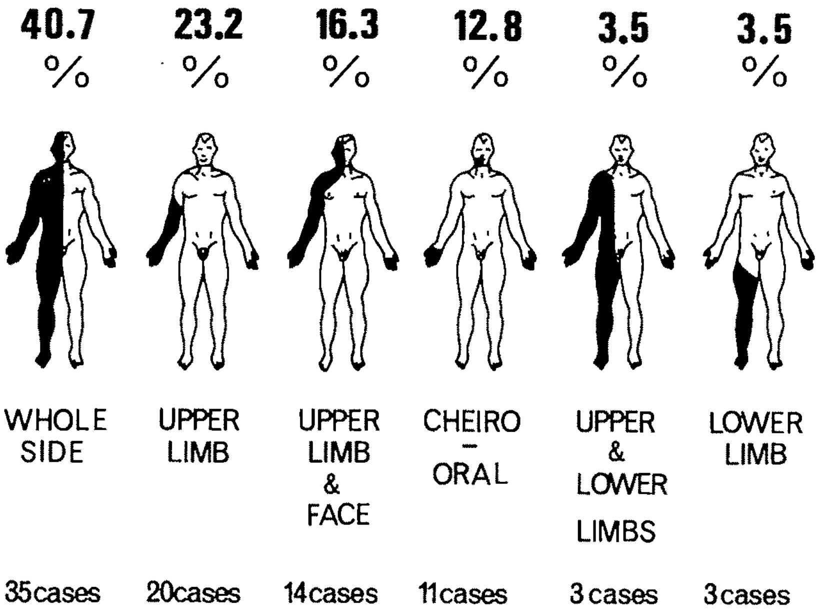


FIG 12. Maximal spread of somatosensory symptoms in 86 patients.

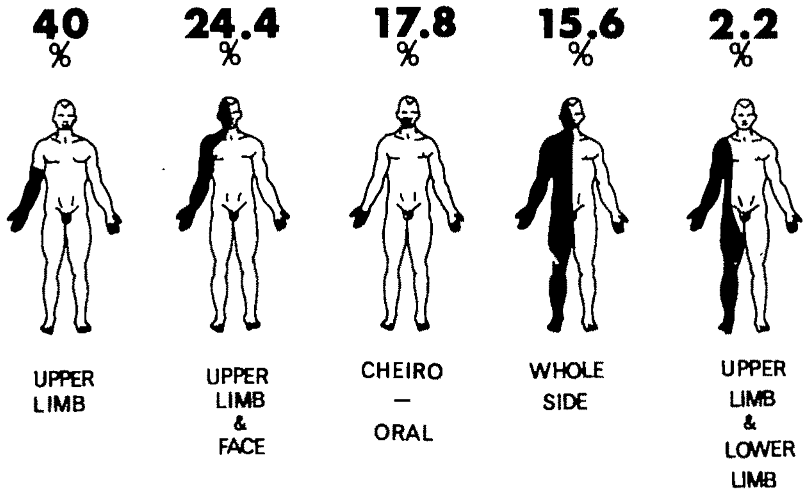


FIG 13 Maximal spread of somatosensory symptoms in 45 patients with seizures beginning in the hand or fingers.

TABLE 3. SUMMARY OF 21 ELECTRO-CLINICAL SEIZURES RECORDED IN 19 PATIENTS*

Case and Index No.	*Side of clinical seizure*	*Duration of clinical somatosensory symptoms (seconds)*	*Type of fit*	*Mode of activation*	*EEG**
1: 125 337	Right	40	Tingling whole upper limb	Hyperventilation	Discharge of spikes beginning 80 s before clinical fit in L. parietal region, spreading to L rolandic region during seizure.
2: 113 118	Left	80	Pins and needles foot→lower limb→upper limb	Hyperventilation	Discharge of spikes in R. rolandic region
3: 137 165	Right	180	Tingling hand→clonic hand→clonic upper limb→upper limb paralysis (15 min)	Hyperventilation	Theta slow waves in L. rolandic region
4: 146 556	Left	20	Pins and needles and pain whole side	Hyperventilation	Rhythmic slow delta waves in R. temporal region
5: 70 387	Right	30	Cramp-like sensation whole upper limb	Hyperventilation	Discharge of rhythmic spikes in L. rolandic region
6: 85 667	Left	480	Tingling hand	Hyperventilation	Discharge of spikes in R. temporal region spreading to R. posterior temporal and occipital regions
7: 88 383	Right	180	Pins and needles hand→right face→clonic thumb	Hyperventilation	Rhythmic spikes in L. posterior temporal region spreading to L. parietal region during seizure. Post-ictal slow delta waves in L. posterior temporal region
8: 98 034	Left	40	Clouding of consciousness, asomatognosia whole upper limb	Bemegride i.v. 2 mg/kg	Rhythmic slow delta waves in L. temporal region, lasting 7 min after end of clinical seizure
9: 105 395	Left	70	Pins and needles and pain hand→forearm	Hyperventilation	Increase of a pre-existing slowing of the whole R. hemisphere
10: 101 858	Left	?	Numbness and hypoæsthesia hand	Bemegride i.v. 1 mg/kg	Rhythmic spike-waves in R. frontal region

11: 77 649	Left	90	Tingling: shoulder→whole upper limb→shivering hand	Bemegride i.v. 2 mg/kg	Spike-waves in R. occipital region spreading to ipsilateral and contralateral rolandic regions
12: 126 232	Left	120	Tingling and burning sensation whole upper limb	Hyperventilation	Rhythmic spikes in R. rolandic region
13: 71 887	Left	60	Pins and needles hand→forearm	Spontaneous	Slow delta waves in R. temporal region
14: 73 330	Right	150	Tingling hand→clonic hand	Hyperventilation	Rhythmic spikes in L. rolandic region spreading to L. parietal region, lasting 10 minutes after end of clinical seizure
15: 114 577	Right	126	Tingling with sensation of cold hand→upper limb lower limb →clonic hand	Hyperventilation	Rhythmic spike waves in L. temporal region spreading to whole hemisphere
16: 120 748	Right	100	Pins and needles foot whole side; painful tonic spasm. Whole side; post-ictal paralysis whole side	Intermittent photic stimulation	Slow delta waves, rhythmic spike-waves in L. parietal region
17: 124 266	Right	140	Clonic hand→pins and needles thumb	Hyperventilation	Rhythmic slow-delta waves in L. rolandic region beginning 12 min before clinical seizure
18: 70 710	Left	60	Pins and needles thumb→clonic hand	Bemegride i.v. 2·5 mg/kg	Rhythmic slow delta waves in R. parietal region spreading to both frontal regions
19: 74 112	Right	30 180 60	Pins and needles, cheiro-oral	Hyperventilation	Discharge of rhythmic spikes→rhythmic spike-waves in L. rolandic region spreading to R. vertex region or Rhythmic spikes in L. temporal region

---

* A precise description of the chronology of the EEG events is given in all cases in which the clinical seizure and the EEG abnormalities were not strictly concomitant.

region in 5 patients. Because of the small number of patients, the localization of the ictal EEG abnormalities could not be correlated with the various patterns of somatosensory seizures. However, 2 out of 5 patients with temporal ictal EEG discharges experienced painful seizures without tonic motor phenomena. In contrast only one patient out of 14 with central EEG discharges was similarly affected. In the only case of left-sided paroxysmal asomatognosia, the ictal EEG pattern was composed of right temporal rhythmic slow-waves.

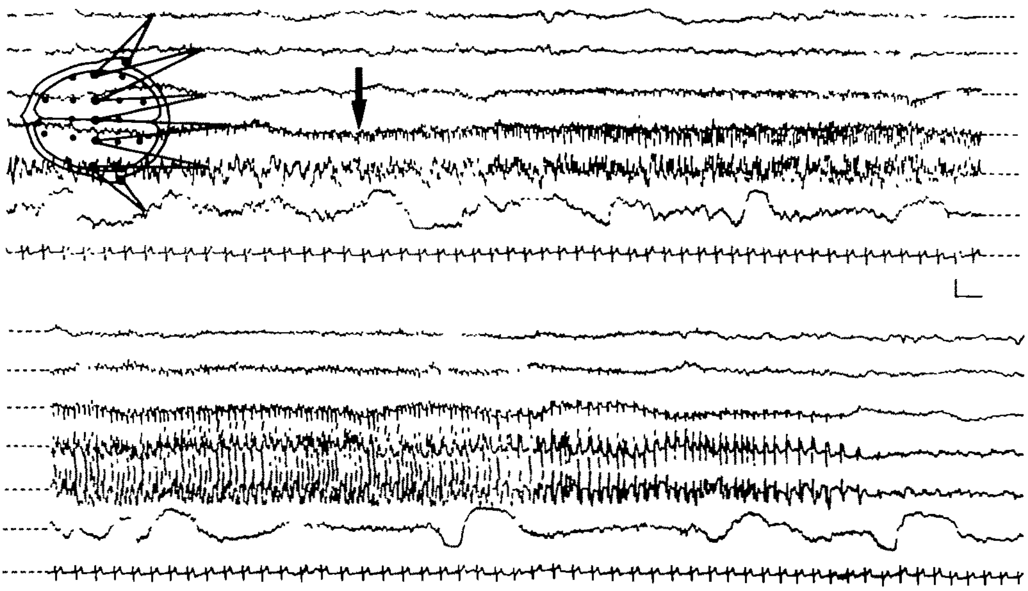


FIG. 14. EEG recordings taken during clinical seizure induced by hyperventilation (Case 74 112). Ictal discharge of spikes, then of spike-waves, in left rolandic region, spreading to right homologous region, during 180 s, with cheiro-oral pins and needles on the right side. Onset of clinical seizure indicated by the arrow Paræsthesiæ ceased with the end of the ictal EEG discharge. Dotted line indicates an interruption of two min during which no modification of the tracing occurred. Records from remaining EEG leads showed no abnormalities, and are omitted from the figure. Calibration 50 mV/1 s.

Ætiology of Somatosensory Epilepsy

The frequency of the different ætiologies is summarized in fig. 15.

In a large number of patients (59) epilepsy was caused by tumours, whose histology was available from operative specimens in all patients (fig. 16). No difference in frequency of tumours between neurological and neurosurgical inpatient populations was noted. In this group of 37 males and 22 females, an increased mean age of onset (43·1 years) was the only feature which could be correlated with the presence of a tumour ($t = 3{\cdot}16$, $P < 0{\cdot}01$). No statistically significant correlation was found between the frequency of tumours and sex of the patient.

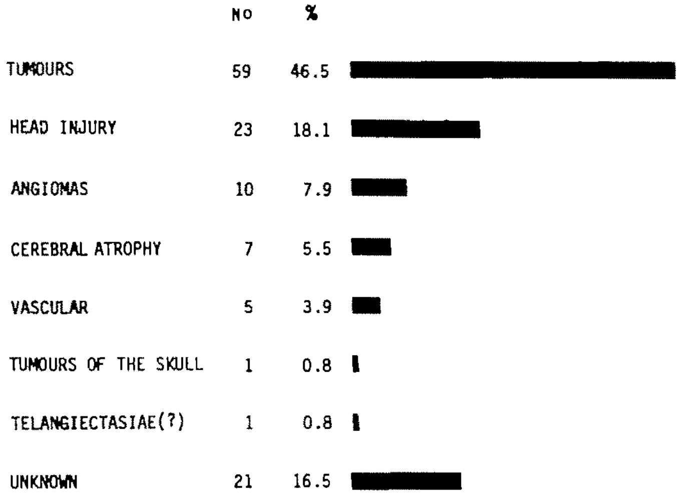


FIG. 15. Ætiology in 127 patients.

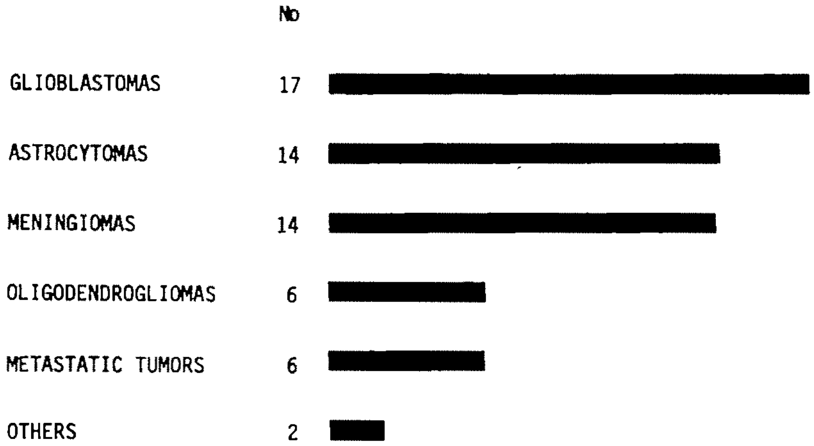


FIG. 16. Histology of tumours in 59 patients.

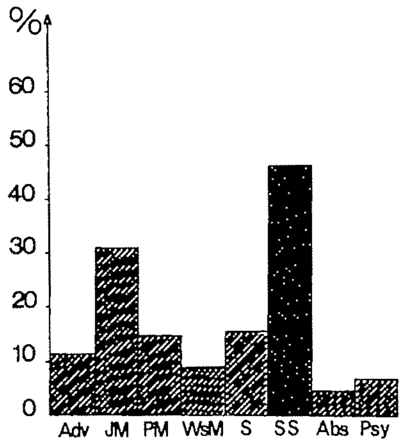


FIG. 17. Frequency of tumours in different types of partial seizures. Abbreviations as in Fig. 8. χ^2 coefficients, calculated with the correction of Yates when necessary, are those obtained by comparing the frequency of tumours in each type of partial seizures with the frequency of tumours in the group of patients with somatosensory seizures

Adversive seizures	461 cases	51 tumours	11·06%—$\chi^2 = 82{\cdot}02$
'Jacksonian' motor seizures	199 cases	62 tumours	31·16%—$\chi^2 = 7{\cdot}14$
Partial tonic or clonic motor seizures	1158 cases	169 tumours	14·59%—$\chi^2 = 79{\cdot}61$
Whole side motor seizures	582 cases	49 tumours	8·42%—$\chi^2 = 113{\cdot}89$
Sensory seizures (auditory, visual, olfactory, gustatory)	262 cases	40 tumours	15·27%—$\chi^2 = 42{\cdot}23$
Somatosensory seizures	127 cases	59 tumours	46 45%
Absences of short duration with automatisms	293 cases	12 tumours	4·10%—$\chi^2 = 110{\cdot}19$
Psychomotor seizures	449 cases	29 tumours	6·46%—$\chi^2 = 119{\cdot}29$

The incidence of tumours was higher in patients with somatosensory seizures than in patients with any of the other types of partial seizures quoted in fig. 17 ($P \leqslant 0{\cdot}01$ for all χ^2 tests); this is also true at the same level of significance if one considers only the patients who were older than 25 years of age when they experienced their first epileptic seizure (fig. 18).

TABLE 4. DURATION OF PRE-OPERATIVE EVOLUTION OF SOMATOSENSORY EPILEPSIES DUE TO TUMOURS (54 CASES)*

Duration (months)	*Metastatic tumours*	*Astrocytomas*	*Glioblastomas*	*Meningiomas*	*Oligodendrogliomas*
Mean value	6·6	37·9	9·0	26·9	44·9
Variance	38·9	979·3	193·8	784·4	1310·5
Standard deviation	6·2	31·3	13·9	28·0	36·2
Minimum	0·8	4·6	0·5	1·0	0·8
Maximum	15·3	99·7	49·7	84·6	102·5
No. of cases	6	14	14	14	6

* Three cases of glioblastoma in which somatosensory epilepsy was related to recurrence of a previously operated tumour are not included in this Table.

The mean duration of the pre-operative evolution of somatosensory epilepsies for the different histological classes of tumours is given in Table 4. The different ictal patterns could not be statistically correlated with the degree of malignancy of the tumours. However, prolonged seizures (lasting longer than ten minutes) were observed only in meningiomas. In the majority (46 cases) somatosensory epilepsy was the first clinical manifestation of the tumour. Occasionally the epileptic disorder began either with generalized tonic-clinic seizures, or with partial somatomotor seizures. Initial examination in a neurology department was considered to be normal in 37 patients with cerebral tumours (63 per cent). All the tumours were supratentorial: two were callosal (reticulosarcoma, one case; lipoma, one case), and the remainder were lateralized.

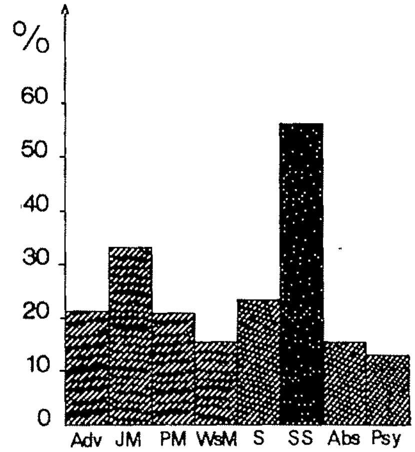


FIG. 18. Frequency of tumours in late onset epilepsies (age 25 years) in the different types of partial seizures. Abbreviations as in Fig. 8. χ^2 coefficients, calculated with the correction of Yates when necessary, are those obtained by comparing the frequency of tumours in each type of partial seizures with frequency of tumours in group of patients with somatosensory seizures.

Adversive seizures	180 cases	38 tumours	21·11%—$\chi^2 = 33{\cdot}8$
'Jacksonian' motor seizures	140 cases	47 tumours	33·57%—$\chi^2 = 11{\cdot}07$
Partial tonic or clonic motor seizures	654 cases	137 tumours	20·95%—$\chi^2 = 53{\cdot}63$
Whole side motor seizures	237 cases	35 tumours	14·77%—$\chi^2 = 58{\cdot}26$
Sensory seizures (auditory, visual, olfactory, gustatory)	148 cases	35 tumours	23·65%—$\chi^2 = 25{\cdot}42$
Somatosensory seizures	98 cases	55 tumours	56·12%
Absences of short duration with automatisms	51 cases	8 tumours	15·69%—$\chi^2 = 20{\cdot}85$
Psychomotor seizures	177 cases	22 tumours	12·43%—$\chi^2 = 57{\cdot}58$

Head injury was the second most frequent ætiology (23 cases) in our series. With three exceptions the injury had been severe, with post-traumatic coma. An intracerebral hæmatoma was surgically evacuated at the time of trauma in 9 patients while 7 patients suffered an hemispheric contusion with a contralateral hemiplegia. In these 16 patients the mean interval between head injury and onset of the somatosensory epilepsy was thirteen months (min. four months, max. nine years). In 4 other patients, the epilepsy was caused by post-traumatic atrophy, purely cortical, limited to the parietorolandic area in 2 cases, and diffuse in the 2 other cases. In the 3 remaining cases, the head injury had been mild, although a subdural hæmatoma had resulted; 2 patients had been operated on before the onset of the epilepsy while in one case, the epilepsy drew attention to the subdural hæmatoma.

In most cases of cerebral angioma (6 cases out of 10) the somatosensory seizures were associated with other epileptic disorders (somatomotor, auditory, psychomotor, or generalized seizures). The longest somatosensory seizures in our series (forty-five minutes) were reported by one of these patients. The angiomas were always very large, and in one case only the centroparietal region could be considered as undamaged on angiographic data.

Excluding the 4 cases of post-traumatic atrophy (*see above*), somatosensory epilepsy due to cerebral atrophy occurred predominantly in young patients (less than 4 years old in 5 cases), who suffered severe motor and mental sequelæ as a result of acute encephalitis or post-anoxic encephalopathy. Nevertheless, cerebral atrophy was diagnosed by pneumo-encephalography in 2 adult patients without any previous history of neurological illness. In all cases, pneumoencephalograms showed diffuse cerebral atrophy, both cortical and subcortical.

In 3 of the 5 patients classified as vascular, an obvious ischæmic lesion of one hemisphere was revealed by the history, radio-isotope scans and carotid angiograms. In one 19-year-old female with a past history of tuberculous meningitis, a stenosis of the left middle cerebral artery as a cause of right cheiro-oral paræsthetic seizures could only be diagnosed tentatively, since the possibility of parenchymatous cicatricial lesions could not be ruled out. In the fifth case a vascular ætiology for the somatosensory epilepsy had been proposed in a male with an atheromatous stenosis of the right internal carotid artery extracranially, after elimination by appropriate investigations of other possible ætiological factors.

Failure to determine the ætiology in a high proportion of cases may be attributed to the limited efficiency of the neuroradiological and isotopic means of investigation which were in use during the ten-year period of this study. Thus, some of these patients may have small non-malignant brain tumours, despite investigations and the minimal one-year period of follow-up required for the selection (*see above*).

DISCUSSION

Clinical and Pathophysiological Analysis

Following the classical distinction between 'simple' and 'complex' somatosensory seizures, our statistical data demonstrate that, in nearly 90 per cent of cases, somatosensory epilepsy is characterized by unilateral elementary paræsthetic seizures of short duration, the hand and the upper limb being involved in most cases. The majority of seizures in our series were of the 'simple' or 'elementary' type, despite the wide range of sensations reported by the patients. Seizures characterized by complex somatognostic illusions are rare (10·2 per cent of cases in our series). Even in this group of patients the paroxysmal disorders of the body schema were often elementary; they never reported such complex hallucinations as those described in all classical reports of parietal lobe epilepsies (Riddoch, 1941; David, Hécaen, Passouant and Talairach, 1946; Critchley, 1953; Hécaen and Ajuriaguerra, 1952; Lhermitte, 1957; Chavany, 1958; Lhermitte and Cambier, 1964).

Analysis of the somæsthetic symptoms shows that almost 40 per cent of our patients experienced a combination of sensations during the seizures. The interpretation of such subjective symptoms may be questioned, since the quality and the precision of the description largely depend on the cultural level and the emotional reactivity of individual patients. This is particularly true for the painful seizures during which pain is associated with paræsthesiæ, thermal sensation, tonic muscular spasm, or somatognostic disturbance in most cases. In painful paræsthetic seizures, even the existence of pain is questionable, 'the degree of pain being so slight as to cause one to wonder if the use of the term is not a misnomer' (Penfield and Jasper, 1954). Some patients reported a painful cramp with tonic muscular spasm; in these cases, we think that pain is a direct consequence of the motor phenomenon, and is not of cortical origin, a view endorsed by Penfield and Gage (1934). But paroxysmal unilateral pains may occasionally be the only manifestation of a cortical lesion of the contralateral hemisphere. Since the first description by Head and Holmes (1911) of pseudoneuralgic pains in a patient with a glioma of the upper and inner aspect of the post-central gyrus, a few cases of 'pure epileptic pains' have been reported in the literature (Penfield and Gage, 1933; Marchand and Ajuriaguerra, 1939; Michelsen, 1943; Penfield and Kristiansen, 1951; Whitty, 1953; Jefferson, 1958; Fine, 1967; Retif, Brihaye and Vanderhaegen, 1967; Wilkinson, 1973). In these observations pain is usually described as pseudoneuralgic, causalgic or pseudothalamic. In the latter type concomitant vasomotor phenomena may be observed as in Whitty's patient (1953). The sparsity of reports of purely painful seizures relates to the extreme rarity of such seizures (1·5 per cent in our series; 4 cases of the 85 cases of traumatic epilepsy studied by Russell and Whitty, 1953). Their existence is, however, of great theoretical importance, and has been quoted as evidence of cortical integration of pain by certain authors (Facon, Wertheim and Mestes, 1960; Wilkinson, 1973; Fields and Adams, 1974).

The spread of paræsthesiæ beginning in the fingers was restricted to the forearm in 40 per cent of our cases, cheiro-oral spread being less common (18 per cent). This characteristic, already noted by Sittig in 1925, was interpreted by Lende and Popp (1976) as being the consequence of an unidirectional spread of the discharge which could not cross the boundaries of 'coherent functional subunities' in SI. According to Lende and Popp (1976) these functional subunities would be the three somatotopic areas representing, respectively, the lower limb, the upper limb and the face on each primary somatosensory area SI. Such an interpretation would be in agreement with the anatomical data of Jones and Powell (1969) in rhesus monkeys, since, in these animals, the intrinsic cortico-cortical connections in SI respect the independence of these three somatotopic areas. But our series does not support such a concept in many cases, especially when the paræsthesiæ began in one lower limb, since the entire ipsilateral half of the body became involved in 71 per cent of these seizures.

Most of the non-somatosensory ictal symptoms observed in our patients were motor phenomena. Russell and Whitty (1953) had already observed that a sensory aura would often progress to motor symptoms and that the converse direction of spread was far less common. According to Penfield and Jasper (1954) these motor symptoms are the consequence of the propagation of the ictal discharge from SI to the somatomotor area 4. In contrast Ajmone Marsan and Ralston (1957), in their analysis of Metrazol-induced seizures recorded electroencephalographically, tried to demonstrate that the spread of an epileptic discharge on the surface of either SI or the primary motor area could produce a combined somatosensory and motor seizure. These authors claimed support for this view from the report of Penfield and Jasper (1954) which demonstrated that stimulation of motor and sensory areas produced, respectively, somatic sensations and tonic or clonic phenomena in 25 per cent of cases. Ajmone Marsan and Ralston (1957) considered that the primary somatomotor and somæsthetic areas can be activated independently of one another during an ictal discharge arising in either of these two cortical areas. Such electrical isolation of the primary somatosensory area from the primary motor area during epileptic seizures seems surprising in view of the strong direct cortico-cortical connections observed in primates between area SI and the somatomotor area, and between area SI and the supplementary motor area (Jones and Powell, 1969). Moreover, the view of Ajmone Marsan and Ralston (1957) is not supported by stereo-EEG recordings of a few somatosensory and motor seizures, which demonstrated that motor phenomena only occur when the epileptic discharge spreads forward from area SI towards area 4 or towards the supplementary motor area on the inner aspect of the frontal lobe (Bancaud and Talairach, 1965; Trottier, 1972). The propagation of the ictal discharge to these pre-central motor areas results in the three seizure patterns we have observed in our series; first, somatosensory and tonic seizures of a whole limb or of one entire side of the body when the discharge abruptly invades a part or all the somatomotor area; second, somatosensory and motor tonic-clonic Jacksonian seizures when the spread of the discharge in the somatomotor area is slow and progressive; and third, paræsthetic and 'postural' seizures of the upper limb when the discharge propagates directly from SI to the supplementary motor area.

In conclusion, we must emphasize the rarity of visual ictal symptoms during somatosensory seizures. This fact, noted previously by Russell and Whitty (1953) and by Ajmone Marsan and Ralston (1957), merits attention since in monkeys Jones and Powell (1969) did not find any direct cortico-cortical connections between somatosensory cortex (areas SI, SII, 5 and 7) and the ipsilateral visual cortex (areas 17-18-19-20-21). A comparable organization in man may be the reason why an epileptic discharge arising in SI rarely spreads towards the visual cortical areas.

Localizing Value of Somatosensory Seizures

The lateralizing value of unilateral simple somatosensory seizures was absolute in our population of patients, since in all cases in which the causal lesion was precisely localized, the contralateral hemisphere was found to be damaged. However, some exceptional cases of unilateral paræsthetic seizures in patients with lesions confined to the ipsilateral hemisphere have been reported (Castaigne *et al.*, 1952; Herskowitz and Swerdlow, 1972). In our only case of secondary bilateral seizure, the paræsthesiæ usually followed a 'circular' march, as in one of the observations of Dechaume *et al.* (1961): they began in the right hand, then passed up to the face and down to the left hand. This patient had a reticulosarcoma of the corpus callosum. In none of our cases was a bilateral seizure caused by a unilateral focal lesion of the upper aspect of the anterior half of the sylvian fissure where area SII is supposed to lie in man (Penfield and Rasmussen, 1950).

The centro-parietal region was damaged in 67·5 per cent of our patients with identified lesions. The most frequent localization outside the centro-parietal region was the temporal lobe. The nature of our cases of somatosensory epilepsy, most of which were due to relatively large lesions, did not allow us to distinguish between pre- and post-rolandic lesions within the centro-parietal region. Such a distinction was possible in Russell and Whitty's (1953) series of post-traumatic epileptic patients.

Attempts at more precise correlation of the different ictal patterns with the localization of lesions demonstrated that seizures with thermal sensation or pain were more frequent when the centro-parietal region was unaffected; but we were unable to correlate positively these two kinds of seizure with a localization of the causal lesion in the temporal lobe. Lewin and Phillips (1952) described a patient who sustained a penetrating gunshot wound in the right parietal region, and experienced painful secondary generalized somatosensory seizures beginning with a deep gnawing pain in the left wrist and hand. In this patient, electrical stimulation of the anterior wall of a diverticulum situated just behind the right post-central gyrus, elicited the painful aura. Removal of this part of the cortex was followed by a disappearance of pain, although episodes of somatosensory seizures persisted. These authors also studied two other patients with lower limb amputation and phantom limb or stump pain, who were improved by removal of small areas of post-central gyrus. They concluded that in these three patients 'pain is associated with activation of the sensory cortex'. This contention was supported by Russell and Whitty (1953) and is supported by our statistical results. However, we must emphasize that electrical stimulation of the sensory cortex often fails to reproduce spontaneous paroxysmal epileptic pain and seems to be more effective in the elicitation of non-epileptic phantom limb pains as observed after amputation (Biemond, 1956; Hamby, 1961). On the basis of clinical and anatomical correlation in a few patients, painful seizures have been considered as symptomatic of lesions of area SII (Biemond, 1956) or of the superior and medial parts of the parietal lobe (Wilkinson, 1973). Penfield and Gage (1933) once succeeded in reproducing the paroxysmal painful sensations reported by one of their patients by stimulation of Brodmann's area 5. In our series we were unable to correlate statistically the occurrence of painful seizures with a lesion of any of these cortical areas.

Similarly we were unable to demonstrate a correlation between the occurrence of thermal seizures and lesions of the second somatosensory area, although Penfield and Jasper (1954) elicited a sensation of cold by electrical stimulation of this area.

In our series of 13 right-handed patients, 6 had complex somatognostic seizures referred to the right side of the body. Five of these patients reported a sensation of swelling of the hand with paræsthesiæ. These results, despite their small numbers, are not in agreement with the pre-eminent role assigned to the minor hemisphere in somatognostic integration. It remains uncertain whether a sensation of swelling associated with paræsthesiæ should be considered as a somatognostic disturbance or not. In our only case of paroxysmal hemiasomatognosia, the seizures were left-sided, as in the case reported by Allen (1954), and concomitant with a rhythmic slow-wave discharge in the right temporal region. The occurrence of complex somatosensory seizures was not statistically correlated with the existence of a posterior parietal lesion in our series. This may be due to our small number of cases, since stereo-EEG recordings have shown that these somatognostic illusions are observed when the epileptic discharge reaches the posterior parietal areas (Trottier, 1972, 2 cases). However, very few complex somatosensory seizures have been elicited by electrical stimulation of the patietal cortex (one case by Penfield and Erickson in 1941, one case by Hécaen and Ajuriaguerra in 1952).

Thus according to our data the clinical analysis of the ictal pattern does not allow a precise localization of the lesion. One ready explanation is that the epileptic discharge can originate at a distance from the causal lesion.

Ætiology

The high frequency of brain tumours is a remarkable feature of somatosensory epilepsy. The percentage of brain tumours in our series (46·5 per cent) is almost the same as that reported by Rasmussen (1975) in his population of 134 patients operated on for somatosensory or combined somatosensory and motor seizures (46 per cent). The incidence of brain tumours in somatosensory epilepsy was found to be higher than in any other kind of partial epilepsy in our series. In view of our selection criteria this percentage of cases with tumour is probably not an artefact. Nevertheless, the lowest values of the χ^2 coefficient were obtained when comparing the frequency of tumours in patients with 'Jacksonian' motor fits and in those with somatosensory fits. Although statistically significant, this difference may be questionable; firstly, because a significant percentage of our patients experienced either sensorimotor fits or somatosensory and Jacksonian motor fits; second, because one cannot be certain of the absence of any brief ictal somatosensory symptoms in all our cases classified in the category of 'Jacksonian' motor fits. The frequency of brain tumours in somatosensory epilepsy may be compared with the 19 per cent of brain tumours observed by Rasmussen (1974) in his series of 1365 patients operated on for focal epilepsy with elementary seizures, and with the mean frequency of 14 per cent of brain tumours in our population of epileptic patients with any type of partial epilepsy.

The mean duration of the pre-operative evolution for each histological type of tumour was found to be comparable with those reported in other statistical studies of epilepsy due to tumours (Penfield, Erickson and Tarlov, 1940; Lund, 1952; Le Blanc and Rasmussen, 1974). However, nearly one-third of our patients (32·2 per cent) had been admitted to a neurological department more than one year after they had their first somatosensory seizure. Better knowledge of this kind of epilepsy, and widespread use of non-invasive means of investigation such as computerized axial tomography, may allow earlier ætiological diagnosis in these patients.

SUMMARY

A population of 127 patients suffering from somatosensory epilepsy has been selected from a total of 8938 epileptic patients and statistically studied in order to give a clinical survey of the seizure patterns and of the natural history of the disease. The localizing value of the different types of ictal somatosensory symptoms and EEG abnormalities, and the relative frequency of the different ætiologies, have been analysed with special care.

In nearly 90 per cent of cases somatosensory epilepsy is characterized by the occurrence of 'simple' seizures, i.e. elementary unilateral paræsthetic seizures of short duration involving the hand and the upper limb in most cases. 'Complex' seizures with somatognostic illusions are exceptional. Ictal motor phenomena, including tonic-clonic Jacksonian fits and tonic postural changes, were frequently found to follow the paræsthesiæ. The lateralizing value of unilateral simple somatosensory seizures was absolute in our patients, but little of significance was found on attempting a more precise correlation between type, duration and localization of the somæsthetic symptoms and the sites of the lesions. However, seizures with thermal sensation or pain were more frequent when the centroparietal region was unaffected, and seizures beginning in the foot were specifically related to parasagittal lesions. The ictal EEG abnormalities recorded in 19 patients could not be correlated with the various patterns of somatosensory seizures.

Of our patients 46·5 per cent had brain tumours. The incidence of tumours was found to be higher in patients with somatosensory seizures than in patients with any other type of partial seizures. The only clinical feature which could be correlated with the presence of a tumour was an increased age at onset of somatosensory seizures. The pre-operative evolution of somatosensory epilepsy due to tumours is described. Next to tumours, head injury, cerebral angiomas, and cortical atrophy were the most frequent ætiologies.

The pathophysiology and the localizing value of somatosensory seizures are discussed.

ACKNOWLEDGEMENTS

The authors are grateful to Professors M. Devic, B. Schott, A. Garde, L. Mansuy, G. Lecuire and G. E. Allegre for permission to use their case records, to Mr. M. Biron for his valuable co-operation in the computerized statistical study, to Professor M. Jeannerod, Dr. D. M. MacDonald, and Mr. H. Kennedy for reading the manuscript, and to Ms M. Matillon and Mr. S. Bello for technical assistance.

REFERENCES

AJMONE MARSAN, C. and RALSTON, B. L. (1957) *The Epileptic Seizure. A Clinical Electrographic Analysis of Metrazol-induced Attacks.* Springfield: Charles C. Thomas, pp. 187-230.

ALLEN, I. M. (1954) Unilateral asomatognosia as a part of the epileptic attack. *New Zealand Medical Journal,* **53,** 142-150.

BANCAUD, J. and TALAIRACH, J. (1965) *La Stéréo-électroencéphalographie dans l'Épilepsie. Informations Neurophysiologiques Apportées par l'Investigation Fonctionnelle Stéréotaxique.* Paris: Masson, pp. 38-49.

—— —— GEIER, S. and SCARABIN, J. M. (1973) *EEG et SEEG dans les Tumeurs Cérébrales et l'Épilepsie.* Paris: Editor, pp. 316-319.

BIEMOND, A. (1956) The conduction of pain above the level of the thalamus opticus. *Archives of Neurology and Psychiatry, Chicago,* **75,** 231-244.

CASTAIGNE, P., HELD, J. and LECABLE, R. (1952) Epilepsie sensitive localisée due à une localisation pariétale ipsilatérale. *Comptes Rendus de la Société Médicale des Hôpitaux de Paris,* **68,** 782.

CHAVANY, J. A. (1958) *Épilepsie. Étude Clinique, Diagnostique, Physiopathogénétique et Thérapeutique.* Paris: Masson, pp. 66-74.

CRITCHLEY, M. (1953) *The Parietal Lobes.* London: Edward Arnold, p. 480.

DAVID, M., HÉCAEN, H., PASSOUANT, J. and TALAIRACH, J. (1946) Asomatognosie partielle et algies paroxystiques, seuls signes d'un angiome pariétal partiellement calcifié. Guérison après extirpation chirurgicale. *Revue Neurologique,* **78,** 236-238.

DECHAUME, J., SCHOTT, B., COURJON, J. and BOURRAT, C. (1961) Crises bilatérales motrices ou sensitives de type Bravais-Jacksonien. *Revue Neurologique,* **104,** 469-478.

FACON, E., WERTHEIM, N. and MESTES, E. (1960) Syndrome d'inattention spatiale avec douleurs d'origine corticale. Etude anatomo-clinique. *Revue Neurologique,* **102,** 61-73.

FIELDS, H. L. and ADAMS, J. E. (1974) Pain after cortical injury relieved by electrical stimulation of the internal capsule. *Brain,* **97,** 169-178.

FINE, W. (1967) Post-hemiplegic epilepsy in the elderly. *British Medical Journal,* **i,** 199-200.

GASTAUT, H. (1954) *The Epilepsies: Electroclinical Correlations.* Springfield: Charles C. Thomas, pp. 8–44.

—— (1969) Clinical and electroencephalographical classification of the epileptic seizures. *Epilepsia,* **10.** Supplement to no. 3, pp. 52–53.

GASTAUT, M. D. and BROUGHTON, R. (1972) *Epileptic Seizures. Clinical and Electrographic Features. Diagnosis and Treatment.* Springfield: Charles C. Thomas, pp. 112–132.

HAMBY, W. B. (1961) Reversible central pain. *Archives of Neurology, Chicago,* **5,** 528–532.

HEAD, H. and HOLMES, G. (1911) Sensory disturbances from cerebral lesions. *Brain,* **34,** 102–254.

HÉCAEN, H. and AJURIAGUERRA, J. (1952) *Méconnaissances et Hallucinations Corporelles. Intégration et Désintégration de la Somatognosie.* Paris: Masson.

HERSKOWITZ, A. and SWERDLOW, M. (1972) Focal seizures: a false lateralizing sign. *Diseases of the Nervous System,* **33,** 523–525.

JACKSON, J. H. (1863) Epileptiform seizures, aura from the thumb, attacks of coloured visions. *Medical Times-Gazette,* **1,** 589–590.

JEFFERSON, G. (1958) Concerning focal seizures commencing in the lower limb. *Laval Medical,* **26,** 482–510.

JONES, E. G. and POWELL, T. P. S. (1969) Connections of the somatic sensory cortex of the Rhesus monkey. I. Ipsilateral cortical connections. *Brain,* **92,** 477–502.

LE BLANC, F. E. and RASMUSSEN, T. H. (1974) Cerebral seizures and brain tumors. In: *Handbook of Clinical Neurology.* Vol. 15. *The Epilepsies.* Amsterdam: North Holland Publishing Company, pp. 295–301.

LENDE, R. A. and POPP, A. J. (1976) Sensory Jacksonian seizures. *Journal of Neurosurgery,* **44,** 706–711.

LEWIN, W. and PHILLIPS, C. G. (1952) Observations on partial removal of the post-central gyrus for pain. *Journal of Neurology, Neurosurgery and Psychiatry,* **15,** 143–147.

LHERMITTE, F. and CAMBIER, J. (1964) *Les Perturbations Somatognosiques en Pathologie Nerveuse.* Rapport au Congrès de Psychiatrie et de Neurologie de langue Française. Paris: Masson.

LHERMITTE, J. (1957) Les algo-hallucinoses. Les hallucinations de la douleur. In: *La douleur et les douleurs.* Edited by Th. Alajouanine. Paris: Masson, pp. 242–258.

LUND, M. (1952) Epilepsy in association with intracranial tumor. *Acta Neurologica Scandinavica,* Suppl. 81, 86–106.

MARCHAND, L. and AJURIAGUERRA, J. (1939) Crises d'épilepsie a aura douloureuse. *Annales Médico-psychologiques,* **97,** 794–796.

MICHELSEN, J. J. (1943) Subjective disturbances of the sense of pain from lesions of the cerebral cortex. *Research Publications of the Association for Nervous and Mental Diseases,* **25,** 86–89.

PENFIELD, W. and ERICKSON, T. C. (1941) *Epilepsy and Cerebral Localization.* Springfield: Charles C. Thomas.

—— —— and TARLOV, I. (1940) Relation of intracranial tumor and symptomatic epilepsy. *Archives of Neurology and Psychiatry, Chicago,* **44,** 300–315.

—— and GAGE, L. (1933) Cerebral localization of epileptic manifestations. *Archives of Neurology and Psychiatry, Chicago,* **30,** 709–727.

PENFIELD, W. and JASPER, H. (1954) *Epilepsy and the Functional Anatomy of the Human Brain.* London: Churchill, pp. 54–102.

—— and KRISTIANSEN, K. (1951) *Epileptic Seizure Patterns. A Study of the Localizing Value of Initial Phenomena in Focal Cortical Seizures.* Springfield: Charles C. Thomas, pp. 36–46.

—— and RASMUSSEN, T. (1950) *The Cerebral Cortex of Man.* New York: Macmillan.

RASMUSSEN, T. (1974) Seizure with local onset and elementary symptomatology. In: *Handbook of Clinical Neurology.* Vol. 15. *The Epilepsies.* Edited by O. Magnus and A. M. Lorentz de Hass. Amsterdam: North Holland, pp. 74–86.

—— (1975) Surgery for epilepsy arising in regions other than the temporal and frontal lobes. In: *Advances of Neurology.* Vol. 8. Edited by D. P. Purpura, J. K. Penry and R. D. Walker. New York: Raven Press, pp. 207–226.

RETIF, J., BRIHAYE, J. and VANDERHAEGEN, J. J. (1967) Syndrome douloureux 'thalamique' et lésion pariétale. A propos de trois observations de tumeurs à localisation pariétale s'étant accompagnées de douleurs spontanées de l'hémicorps controlatéral. *Neuro-chirurgie,* **13,** 375–384.

RIDDOCH, G. (1941) Phantom limbs and body shape. *Brain,* **64,** 197–222.

RUSSELL, W. R. and WHITTY, C. W. M. (1953) Studies in traumatic epilepsy 2. Focal motor and somatic sensory fits: a study of 85 cases. *Journal of Neurology, Neurosurgery and Psychiatry,* **16,** 73–97.

SITTIG, O. (1925) A clinical study of sensory Jacksonian fits. *Brain,* **48,** 233–254.

TROTTIER, S. (1972) *Séméiologie clinique des accès épileptiques à point de départ rolandique.* Thèse de mèdecine, Paris.

WHITTY, C. W. M. (1953) Causalgic pain as an epileptic aura. *Epilepsia,* **2,** 37–41.

WILKINSON, H. A. (1973) Epileptic pain: an uncommon manifestation with localizing value. *Neurology, Minneapolis,* **23,** 518–620.

(*Received August 16, 1977*)

Brain (1978), **101**, 333-344

SUBACUTE SPONGIFORM ENCEPHALOPATHY (CREUTZFELDT-JAKOB DISEASE)

THE NATURE AND PROGRESSION OF SPONGIFORM CHANGE

by C. L. MASTERS *and* E. P. RICHARDSON JR.

(*From the Charles S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital, and the Departments of Neurology-Neuropathology, Harvard Medical School, Boston*)

INTRODUCTION

CREUTZFELDT-JAKOB disease (CJD) is now classified as one of two types of subacute spongiform encephalopathy which are transmissible (Gibbs and Gajdusek, 1973), and is an example of a virus-induced slow degeneration of the brain. While the demonstration of transmissibility has become the definitive criterion for diagnosis, there remains considerable disagreement over the clinical and pathological features which permit a diagnosis in the individual case (Traub, Gajdusek and Gibbs, 1977). Part of this difficulty arises from a general tendency to identify spongiform change with status spongiosus. Failure to distinguish between these two terms and to characterize the lesions more precisely has led to considerable confusion, particularly in the literature before 1968, when the transmissible nature of this disease was first demonstrated (Gibbs, Gajdusek, Asher, Alpers, Beck, Daniel and Matthews, 1968). The special significance of spongiform change, as being specific for these diseases, has been further emphasized by the neuropathological features of the experimentally transmitted disease, since all cases so far transmitted have produced this change in the experimental animals (Beck, Daniel, Matthews, Stevens, Alpers, Asher, Gajdusek and Gibbs, 1969; Masters, Kakulas, Alpers, Gajdusek and Gibbs, 1976). Moreover, spongiform change has been present in all of the human cases of CJD which have transmitted (Traub *et al.*, 1977).

The object of this paper is to re-examine the nature of spongiform change and status spongiosus in CJD, to define their light microscopic appearances, and to examine the relationship between the distribution and severity of the lesions and the duration of clinical illness.

MATERIALS AND METHODS

Seventeen cases (Cases 1-17, Table 1) of CJD were available in the files of the C. S. Kubik Laboratory of Neuropathology, Massachusetts General Hospital; four cases (Cases 18-21, Table 1) were obtained from the Boston VA Hospital. The criteria used for inclusion of cases in this summary were based on a clinical history of progressive dementia with myoclonus. Representative sections of cerebral cortex, caudate, putamen, globus pallidus, thalamus, hippocampus, brain-stem, cerebellum and spinal cord, stained with hæmatoxylin and eosin (H&E), and cresyl violet were available in most instances. After labels on the slides had been masked in order to prevent identification of the cases, the degrees, respectively, of neuronal loss, gliosis and spongiform change were graded on a five-point scale as follows: ±(½) = possible; +(1) = mild but definite; ++(2) = moderate; +++(3) = severe; ++++(4) = very severe pathological change (the slides were graded independently by one of us, E.P.R., Jr.). The overall score for each area was obtained by summation of the individual scores of each case, and expressed as a percentage of the total score obtained over the total attainable score (Table 2). Summation of the scores for each of the three pathological changes in each case was expressed similarly, and was used as an indicator of the severity of the pathological change in each case (Fig. 3).

The course of the illness was subdivided into a prodromal phase and a dementing and/or myoclonic phase. Although this division was somewhat arbitrary, it was necessary because of the difficulty in determining the precise time of onset, which often began with ill-defined neuropsychiatric symptoms. The dementing and/or myoclonic phase usually coincided with the time of the first hospital admission. The following clinical features, selected according to the criteria of Traub *et al.* (1977), were assessed: behavioural disturbance, higher cortical dysfunction, upper and lower motor neuron signs, basal ganglia disorder, myoclonus, cerebellar dysfunction, visual disturbance, seizures and characteristic EEG changes.

RESULTS

The clinical data are summarized in Table 1. There was no sex bias, and the average age at onset was similar to that in the 56 transmissible cases of Traub *et al.* (1977). Prodromal symptoms were usually of less than two months' duration. In one patient (Case 11), there was a six-month history of a Parkinsonian-like syndrome. Case 21 had a history of alcoholism, and presented with a nine-month history of ataxia. Case 15 had the longest duration: thirty-six months. This patient, after an initial rapid decline of higher cortical functions with prominent myoclonus, remained in what was described as a state of decorticate rigidity for two-and-a-half years. Myoclonus developed in all cases, but there was none in which lower motor neuron signs appeared. One patient (Case 16) presented with an incidental severe hypothyroidism; in this case myoclonic movements were slight and occurred only as a terminal feature (Case records of the Massachusetts General Hospital, 1977).

The EEG showed characteristic periodic sharp-wave discharges in 15 cases. In 2 cases (Cases 11 and 12), the EEG was reported as abnormal but was not available for review. In 3 other cases (Cases 1, 15, 17), the EEG was normal, but these recordings had been taken less than ten weeks after the onset of initial symptoms.

Initial review of the histopathological sections drew attention to two distinct types of spongy lesions affecting the grey matter. First, there was the typical spongiform change that was emphasized by Jacob, Eicke and Orthner (1958), Jones

TABLE 1. CLINICAL FEATURES OF 21 CASES OF CJD (AFTER TRAUB *ET AL.*, 1977)

Case No.	*Sex*	*Age at onset (years)*	*Duration of 'prodromal' symptoms (months)*	*Duration of dementing/ myoclonic phase (months)*	*Behavioural disturbance*	*Higher cortical dysfunction*	*Upper motor neuron signs*	*Lower motor neuron signs*	*Basal ganglia disorder*	*Myoclonus*	*Cerebellar dysfunction*	*Visual disturbance*	*Characteristic EEG*	*Seizures*
1	F	69	1	2	+	+	+	—	—	+	+	—	—	—
2	F	53	1½	7	+	+	+	—	+	+	+	+	+	—
3	F	62	¾	1	+	+	+	—	—	+	—	+	+	+
4	F	64	½	1½	—	+	—	—	—	+	—	+	+	—
5	F	50	1¾	2	—	+	+	—	—	+	—	+	+	—
6	M	61	1½	4¾	+	+	+	—	+	+	+	—	+	—
7	F	58	1	¾	+	+	+	—	—	+	+	+	+	—
8	M	49	1¾	1	+	+	+	—	+	+	+	—	+	+
9	M	60	1¼	3	+	+	+	—	—	+	+	—	+	+
10	M	39	1	11¼	+	+	+	—	—	+	—	—	+	—
11	F	61	6	3	+	+	+	—	+	+	—	—	+	+
12	M	69	1	½	+	+	—	—	—	+	—	—	+	+
13	M	59	1½	1½	—	+	+	—	—	+	—	+	+	—
14	M	59	½	4½	+	+	+	—	—	+	—	+	+	+
15	F	60	1	35	—	+	+	—	—	+	+	—	—	—
16	F	72	2	2½	+	+	+	—	—	+	+	+	+	+
17	F	62	6	1	+	+	—	—	—	+	+	—	—	+
18	M	61	1	8	+	+	+	—	+	+	+	—	*	—
19	M	71	1	¾	+	+	+	—	+	+	—	—	+	—
20	M	66	½	4	+	+	+	—	—	+	—	+	+	—
21	M	56	9	4	—	+	—	—	—	+	+	—	+	—

* Data not available. Cases 1, 6, 8, 9, 10, 14 and 15 have been previously reported by Kirschbaum (1968), and correspond to his case numbers VI, VII, III, V, IV, XV and XVI.

and Nevin (1954) and Nevin, McMenemey, Behrman and Jones (1960), and was probably present in Jakob's original fifth case (Jakob, 1923). This lesion was of variable intensity, and is illustrated in fig. 1. This spongiform change was therefore defined as the presence of small vacuoles in the neuropil, usually round or ovoid, occasionally confluent, and were not within the cytoplasmic soma of any of the cells (as seen by light microscopy). These vacuoles were not in a pericellular distribution. The second type of spongy lesion was that of status spongiosus. This lesion was characterized by the appearance of cavitation of the neuropil in the presence of a dense glial meshwork. The cavitation was situated between glial fibres, and the cavities were of irregular size and shape. This lesion (fig. 2) corresponds to what was originally described by Probst (1903), Fischer (1911) and Spielmeyer (1922). Both types of spongy state were well seen in H&E stains, but would have been easily overlooked in sections stained by the Nissl (cresyl violet) method.

The results of the quantitative assessment of the overall distribution of the pathological lesions are summarized in Table 2. The topographic areas are arranged in decreasing order of overall severity. The cerebral cortex was affected by neuronal loss, gliosis or spongiform change in all cases. In 4 cases (Cases 1, 2, 8 and 9) the occipital, frontal or parietal areas tended to be more affected than the temporal region. Involvement of the occipital lobes in the absence of lesions elsewhere in the cerebral cortex was not observed. In some cases the deeper layers

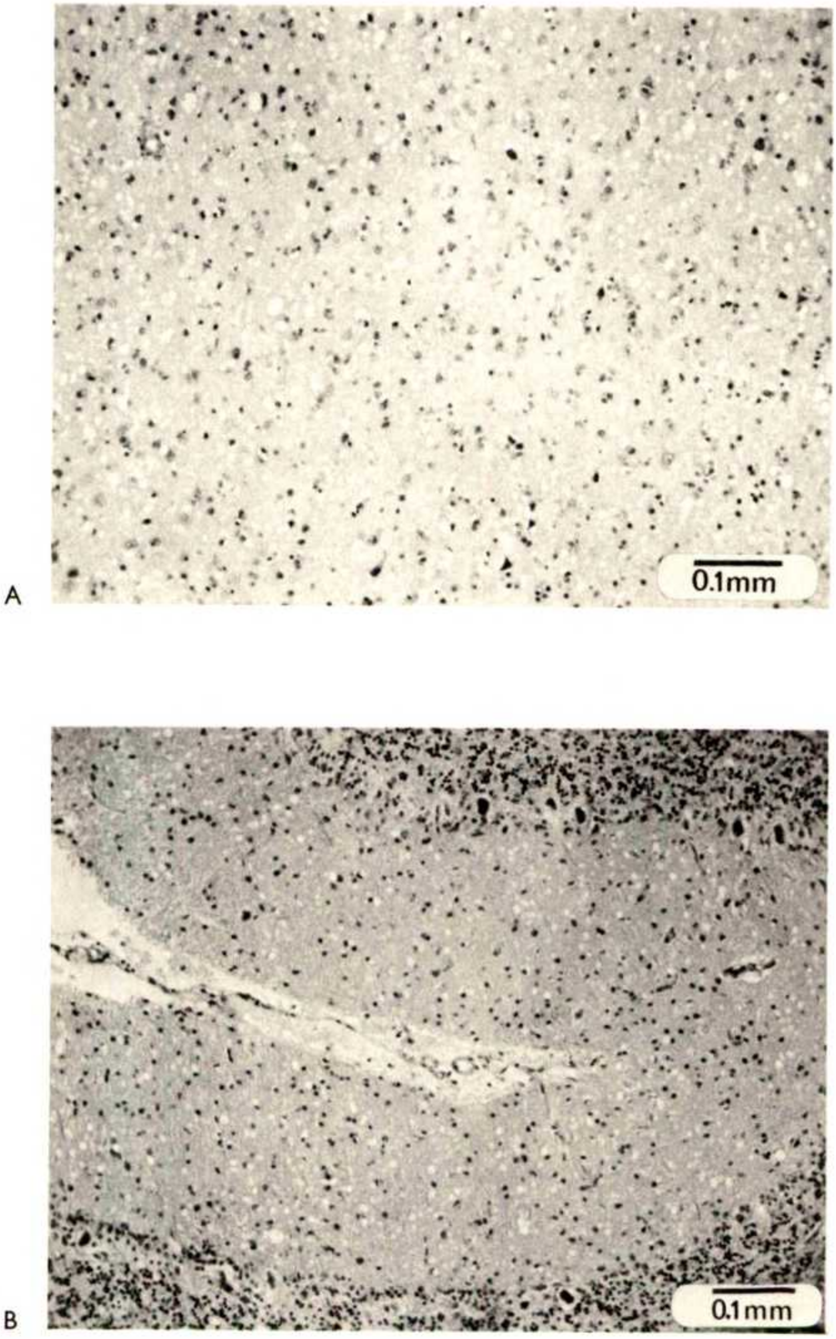


FIG. 1. Severe (grade 3 out of 4) spongiform change. A, occipital cortex and B, cerebellum from Case 16. Hæmatoxylin and eosin.

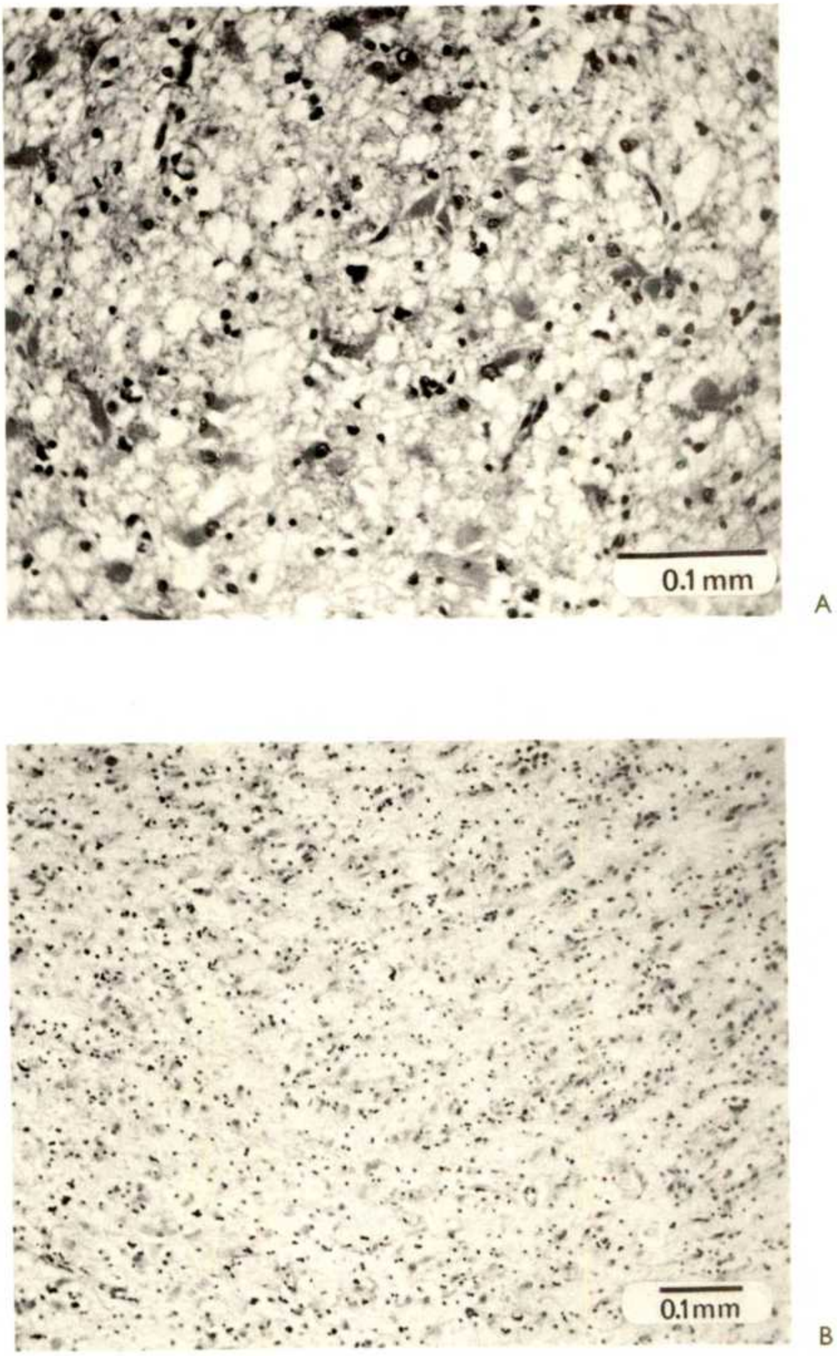


FIG. 2. Status spongiosus with severe gliosis. A, occipital cortex of Case 20 and B, Case 18. Hæmatoxylin and eosin.

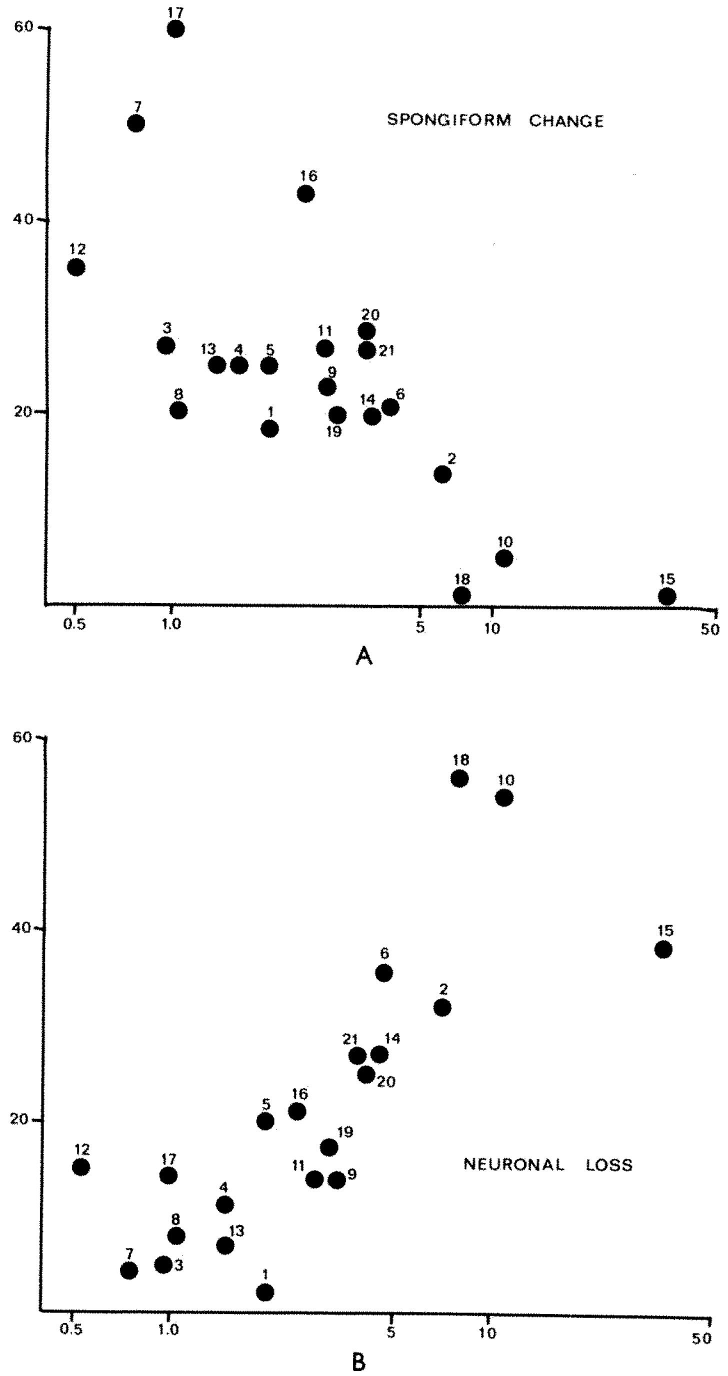
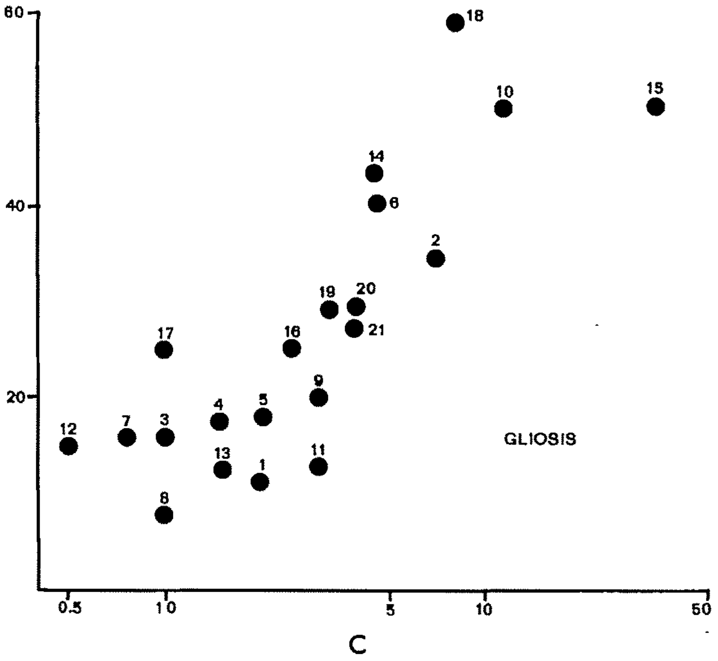


FIG. 3. Overall pathological scores of degree of spongiform change (A), neuronal loss (B), and gliosis (C) in 21 cases of CJD (case numbers are indicated in the figs.). The vertical axis is the percentage score (*see* Methods) and the horizontal axis is the duration (in months) of the dementing/myoclonic phase of the illness.



of cortex were more involved than the superficial layers, although this distinction became less obvious in the longer surviving cases. An occasional feature was the relative sparing of large pyramidal cells in the presence of otherwise severe neuronal loss.

TABLE 2. OVERALL PATHOLOGICAL SCORES[1] FOR REGIONAL AREAS OF BRAIN, ARRANGED IN DESCENDING ORDER OF SEVERITY

	Degree of neuronal loss	*Degree of gliosis*	*Degree of spongiform change*
Cerebral cortex	45/84 (54)	52/84 (62)	41/84 (49)
Dorsomedial nucleus of the thalamus	22/48 (47)	24/48 (50)	10/48 (22)
Caudate and putamen	19/76 (26)	32/76 (42)	36/76 (48)
Cerebellum	25/80 (32)	22/80 (27)	24/80 (31)
Anterior nuclear group of thalamus	7/44 (16)	13/44 (31)	9/44 (22)
Ventral lateral nucleus of thalamus	4/48 (9)	13/48 (37)	5/48 (11)
Hippocampus	0·5/76 (<1)	3/76 (4)	11/76 (15)
Globus pallidus	0·5/56 (1)	4/56 (7)	1/56 (2)
Midbrain	0/60 (0)	2·5/60 (4)	5/60 (8)
Pons	0/72 (0)	0/72 (0)	0/72 (0)
Medulla	0/72 (0)	0/72 (0)	0/72 (0)
Spinal cord	0/52 (0)	0/52 (0)	0/52 (0)

[1] Scores expressed as the total observed over total attainable. Percentage in parenthesis. The degree of neuronal loss, gliosis or spongiform change was graded on a five-point scale, with a maximum score in any individual area of the brain being 4 (*see* Methods). The variability in the total attainable scores reflects the number of cases in which the appropriate area of the brain was available for examination. The scores expressed as percentages give an indication of the distribution of the lesions within the brain, but, as seen in fig. 3, the duration of clinical disease must also be taken into account.

The dorsomedial nucleus of the thalamus, the caudate, and the putamen were the next most affected structures. Gliosis and neuronal loss were prominent in the dorsomedial nucleus, while spongiform change was more prominent in the striatum. The cerebellum was affected in nearly all cases, the spongiform change being found only in the molecular layer. The degree of cerebellar involvement was mild in comparison to the severity of the lesions found in the cerebral cortex, dorsomedial nucleus of the thalamus and striatum (Table 2). Loss of Purkinje cells was not a feature, even in the presence of severe loss of granule cells. The dentate nucleus was not affected in any case.

In the hippocampus, the subiculum was affected, particularly in the longer surviving cases. Here, there was a gradual progression of the spongiform change and gliosis from the more severely affected neopallial cortex of the temporal lobe into the entorhinal area, then subiculum. Ammon's horn and the dentate gyrus were not involved in any case.

No spongiform change was found in the globus pallidus, although gliosis was seen in cases of long survival (more than five months after the onset of the dementing/myoclonic illness). A slight spongiform change was found rarely in the substantia nigra, superior and inferior colliculi. Definite lesions were not seen in the nuclear structures of the pons, medulla, or spinal cord. Secondary corticospinal tract degeneration was observed in the longer surviving cases.

The temporal progression of these lesions is illustrated in fig. 3 where the overall severity of each of the three pathological lesions in each case are arranged in order of survival from the onset of the dementing/myoclonic phase of the illness. In cases surviving less than five months the spongiform change is the prominent feature. In cases surviving longer, neuronal loss and gliosis predominate. In Cases 2, 10, 15, and 18, there was no definite spongiform change remaining in the cerebral cortex, but status spongiosus was present. In Case 2, moderate (+ +) spongiform change was present only in the striatum. In Case 10, spongiform change was graded as possible (±) in the cerebral cortex, cerebellum and subiculum. In Cases 15 and 18, definite spongiform change was not seen in any area.

In Case 16, the degree of spongiform change may have been abnormally high, when compared to the progression of this lesion as seen in the other cases (fig. 3A). This case was clinically unusual because of severe hypothyroidism.

DISCUSSION

The nosology of subacute spongiform encephalopathy with respect to the syndromes described by Creutzfeldt (1921) and Jakob (1921*a*, *b*, 1923) has been a point of contention, particularly in the English literature since 1954, when Jones and Nevin first proposed a new disease entity of subacute vascular encephalopathy. The comparatively recent demonstration of the transmissibility of subacute spongiform encephalopathy has, however, tended to support the unitary nature of the various clinical syndromes which hitherto had been grouped under the heading of CJD. The possible exception to this grouping is the ill-defined amyotrophic form of CJD (Meyer, 1929; Davison and Rabiner, 1940).

Prior to the demonstration of the transmissibility of this disease, the pathological criteria for diagnosis were obscure, particularly because the significance of the various types of spongy lesion was not understood. However, with the knowledge of the characteristic and consistent spongiform change that is produced in the experimental animal (Beck *et al.*, 1969; Masters *et al.*, 1976) it is possible to review the pathological changes in the human disease. It is seen from the present study that previous authors did not distinguish between spongiform change and status spongiosus, and in many instances did not identify the former. This is brought out in our evaluation of 7 cases which Kirschbaum (1968) had previously reported. Of these 7 cases, all but one, according to our criteria, showed varying degrees of spongiform change. In Case 15, where there was no spongiform change, Kirschbaum correctly identified the presence of status spongiosus. Yet in some of the other cases (Cases 6, 8, 10, 14), he did not identify either spongiform change or status spongiosus.

The results of the present study demonstrate the differences between spongiform change and status spongiosus, and the relationship of these lesions to the duration of illness. Spongiform change is the prominent feature in cases dying soon after the onset, and decreases in intensity through the course of the illness to the extent that it may disappear in cases of long survival. This feature may be of importance when a cortical biopsy is examined from a patient suspected of having CJD. Case 16 in the present series was of interest because the degree of spongiform change was possibly increased, when compared to the progression of this change seen in the other cases (fig. 3A). The occurrence of severe hypothyroidism in this case raises the possibility that the metabolic state retarded the natural progression of the spongiform change.

The variation in degree of spongiform change, occurring in a temporal sequence, may also occur in a topographical distribution. With increasing duration of illness, the areas of brain prominently affected with spongiform change in the early phases (especially the cortical mantle) may show a diminution of spongiform change, while the degree of spongiform change in other areas (cerebellum, subiculum and dorsomedial nucleus of thalamus) may increase. In the present series of cases, however, this topographical dispersion was not as clearly definable as the overall temporal progression. The findings are consistent with the data derived from experimental studies (Masters *et al.*, 1976), but a larger series of cases would be required to establish the validity of this observation in humans.

Is the spongiform change pathognomonic? Jellinger and Seitelberger (1970) list a number of conditions in which 'spongy alteration' occurs, including CJD. These encompass the various forms of cerebral 'œdema', toxic encephalopathies, metabolic states such as thiamine deficiency and hepatic encephalopathy, and Canavan's disease. They point out that such 'spongy alterations' may progress to status spongiosus. In our experience, the spongy alteration seen in these varied conditions is quite different from the spongiform change of CJD. The one condition which may cause diagnostic confusion is that of preparative and fixation artefact. Artefactual vacuolation is, however, usually of a pericellular distribution.

Based on the observations of the experimental and naturally occurring spongiform change as discussed above, and on the observation that a spongiform cytopathic effect is seen in cultured brain cells in the outgrowth from explanted brain tissue (Espana, Gajdusek, Gibbs and Lock, 1976), it is concluded that the spongiform change is pathognomonic. The absence of spongiform change, however, does not necessarily preclude the diagnosis of CJD, since, as demonstrated in this paper, the specific vacuolation may not be found in cases with exceptionally long duration of clinical disease. In such cases, the diagnosis of CJD must rest on a typical clinical history, with progressive dementia and myoclonus as prominent features. In the final analysis, the definitive diagnosis remains in the demonstration of a transmissible agent by use of nonhuman primate inoculation. In this respect, of the 21 cases reported in this paper, specimens of fresh frozen brain from 6 cases (Cases 3, 5, 12, 18, 19, 20) were sent to Drs. D. C. Gajdusek and C. J. Gibbs Jr. of the National Institutes of Health, for inoculation into nonhuman primates. The animals inoculated included squirrel, mangabey, capuchin, African green, and rhesus monkeys and chimpanzees. All 6 cases were successfully transmitted to one or more of these nonhuman primates, with incubation periods ranging from fourteen to sixty-six months (Traub *et al.*, 1977). Furthermore, the transmitted disease showed spongiform change in all the animals. These results confirm the unitary nature of the disease process described in this paper, particularly since in Case 18 no definite spongiform change was found. Failure of transmission of Case 18 would otherwise have raised a serious doubt on the validity of grouping these 21 cases together.

The relationship between the virus and the vacuolation remains uncertain. Ultrastructural studies of the spongiform change localize the vacuoles to neurons, dendrites, and occasionally astrocytes (Lampert, Gajdusek and Gibbs, 1971, 1975). Several groups have reported virus-like particles, but usually not in association with the vacuoles (Vernon, Horta-Barbosa, Fuccillo, Sever, Baringer and Birnbaum, 1970; Bots, De Man and Verjaal, 1971; Narang, 1975; De Reuck, De Coster, Otte and Vander Eecken, 1976). Also, virus-like particles are not found consistently, and are not seen in the experimental infection (Traub *et al.*, 1977). The spongiform change therefore remains as an unexplained pathognomonic feature in this group of virus-induced slow degeneration of the brain.

SUMMARY

In 21 cases of human subacute spongiform encephalopathy (Creutzfeldt–Jakob disease), the relative degrees of spongiform change, neuronal loss, and gliosis were quantitated, and examined in relation to the duration of clinical illness. Patients in whom death occurred less than five months after the onset of progressive

dementia and myoclonus had quantitatively more spongiform change than neuronal loss or gliosis. In patients who survived more than five months, neuronal loss and gliosis predominated, while the degree of spongiform change decreased. A morphological distinction was drawn between spongiform change, which is characteristic of the spongiform encephalopathies, and status spongiosus, which is nonspecific, and characteristically is the manifestation of end-stage gliosis. Spongiform change was identified as the presence of small, round or ovoid vacuoles within the neuropil, whereas status spongiosus was characterized by irregular cavitation of the neuropil in the presence of a dense glial meshwork. The distinction of these two types of 'spongy alteration' may help in clarifying the criteria used in the histological diagnosis of subacute spongiform encephalopathy.

ACKNOWLEDGEMENT

We are grateful to Drs. F. Romanul and R. Rosales for permission to include four cases from the Boston VA Hospital. Address reprint requests to Dr. Colin L. Masters, Building 36, Room 5B-25, National Institutes of Health, Bethesda, Maryland 20014, U.S.A.

REFERENCES

Beck, E., Daniel, P. M., Matthews, W. B., Stevens, D. L., Alpers, M. P., Asher, D. M., Gajdusek, D. C. and Gibbs, C. J. Jr. (1969) Creutzfeldt-Jakob disease: the neuropathology of a transmission experiment. *Brain*, **92**, 699–716.

Bots, G. Th. A. M., De Man, J. C. H. and Verjaal, A. (1971) Virus-like particles in brain tissue from two patients with Creutzfeldt-Jakob disease. *Acta Neuropathologica, Berlin*, **18**, 267–270.

Case records of the Massachusetts General Hospital (1977) *New England Journal of Medicine*, **297**, 930–937.

Creutzfeldt, H. G. (1921) Über eine eigenartige herdförmige Erkrankung des Zentralnervensystems. *Histologische und Histopathologische Arbeiten über die Grosshirnrinde*, **6**, 1–48.

Davison, C. and Rabiner, A. M. (1940) Spastic pseudosclerosis. *Archives of Neurology and Psychiatry*, **44**, 578–598.

De Reuck, J., De Coster, W., Otte, G. and Vander Eecken, H. (1976) Papova virus-like particles in a nigral type of Creutzfeldt-Jakob disease. *Journal of Neurology*, Berlin, **213**, 179–188.

Espana, C., Gajdusek, D. C., Gibbs, C. J. Jr. and Lock, K. (1975/76) Transmission of Creutzfeldt-Jakob disease to the Patas Monkey (*Erythrocebus patas*) with cytopathological changes in *in vitro* cultivated brain cells. *Intervirology*, **6**, 150–155

Fischer, O. (1911) Der spongiose Rindenschwund, ein besonderer Destruktionsprozess der Hirnrinde. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **7**, 1–33.

Gibbs, C. J. Jr. and Gajdusek, D. C. (1973) Experimental subacute spongiform virus encephalopathies in primates and other laboratory animals. *Science*, **182**, 67–68.

—— —— Asher, D. M., Alpers, M. P., Beck, E., Daniel, P. M. and Matthews, W. B. (1968) Creutzfeldt-Jakob disease (spondiform encephalopathy): transmission to the chimpanzee. *Science*, **161**, 388–389.

Jacob, H., Eicke, W. and Orthner, H. (1958) Zur Klinik und Neuropathologie der subakuten präsenilen spongiösen Atrophien mit dyskinetischem Endstadium. *Deutsche Zeitschrift für Nervenheilkunde*, **178**, 330-357.

Jakob, A. (1921*a*) Über eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Befunde (Spastische Pseudosklerose-Encephalomyelopathie mit disseminierten Degenerationsherden). *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **64**, 147-228.

—— (1921*b*) Über eine der multiplen Sclerose klinisch nahestehende Erkrankung des Centralnervensystems (spastiche, Pseudosklerose) mit bemerkenswertem anatomischen Befunde. *Medizinische Klinik*, **17**, 372-376.

—— (1923) *Die Extrapyramidalen Erkrankungen*, Berlin: Springer, pp. 218-245.

Jellinger, K. and Seitelberger, F. (1970) Spongy degeneration of the central nervous system in infancy. *Current Topics in Pathology*, **53**, 90-160.

Jones, D. P. and Nevin, S. (1954) Rapidly progressive cerebral degeneration (subacute vascular encephalopathy) with mental disorder, focal disturbances and myoclonic epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 148-159.

Kirschbaum, W. R. (1968) *Jakob-Creutzfeldt Disease*. New York: Elsevier.

Lampert, P. W., Gajdusek, D. C. and Gibbs, C. J. Jr. (1971) Experimental spongiform encephalopathy (Creutzfeldt-Jakob disease) in chimpanzees: electron microscopic studies. *Journal of Neuropathology and Experimental Neurology*, **30**, 20-32.

—— —— —— (1975) Pathology of dendrites in subacute spongiform virus encephalopathies. *Advances in Neurology*, **12**, 465-470.

Masters, C. L., Kakulas, B. A., Alpers, M. P., Gajdusek, D. C. and Gibbs, C. J. Jr. (1976) Preclinical lesions and their progression in the experimental spongiform encephalopathies (kuru and Creutzfeldt-Jakob disease) in primates. *Journal of Neuropathology and Experimental Neurology*, **35**, 593-605.

Meyer, A. (1929) Über eine der amyotrophischen Lateralsklerose nahestehende Erkrankung mit psychischen Störungen. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **121**, 107-138.

Narang, H. K. (1975) Virus-like particles in Creutzfeldt-Jakob biopsy material. *Acta Neuropathologica, Berlin*, **32**, 163-168.

Nevin, S., McMenemey, W. H., Behrman, S. and Jones, D. P. (1960) Subacute spongiform encephalopathy—a subacute form of encephalopathy attributable to vascular dysfunction (spongiform cerebral atrophy). *Brain*, **83**, 519-564.

Probst, M. (1903) Ueber durch eigenartigen Rindenschwund bedingten Blödsinn. *Archiv für Psychiatrie und Nervenkrankheiten*, **36**, 762-792.

Spielmeyer, W. (1922) *Histopathologie des Nervensystems*. Berlin: Springer.

Traub, R., Gajdusek, D. C. and Gibbs, C. J. Jr. (1977) Transmissible virus dementia: the relation of transmissible spongiform encephalopathy to Creutzfeldt-Jakob disease. In: *Aging and Dementia*. Edited by M. Kinsbourne and L. Smith. Flushing, New York: Spectrum Publications, pp. 91-172.

Vernon, M. L., Horta-Barbosa, L., Fuccillo, D. A., Sever, J. L., Baringer, J. R. and Birnbaum, G. (1970) Virus-like particles and nucleoprotein-type filaments in brain tissue from two patients with Creutzfeldt-Jakob disease. *Lancet*, **i**, 964-966.

(*Received September 20, 1977*)

Brain (1978), **101**, 345–368

ACETYLCHOLINE RECEPTORS AND END-PLATE ELECTROPHYSIOLOGY IN MYASTHENIA GRAVIS

by Y. ITO, R. MILEDI, A. VINCENT *and* J. NEWSOM-DAVIS

(*From the Department of Biophysics, University College London, Gower Street, London WC1E 6BT and the Batten Unit, National Hospital for Nervous Diseases, Queen Street, London WC1N 3BG*)

IN electrophysiological studies of intercostal muscle taken at biopsy from patients with myasthenia gravis Elmqvist, Hofmann, Kugelberg and Quastel (1964) found that the miniature end-plate potentials (m.e.p.ps), caused by the release of single quanta of acetylcholine (ACh) from the motor nerve terminal, were smaller than normal. On repetitive stimulation, the end-plate potential (EPP) progressively decreased in amplitude becoming insufficient to bring the membrane potential of the muscle fibre to the critical firing threshold after the first few stimuli, but the quantal content of the EPPs was claimed to be normal. Since postsynaptic sensitivity to carbachol and decamethonium added to the bath solution also appeared to be normal these observations seemed to point to a presynaptic abnormality: namely a decrease in the amount of ACh contained in the individual quanta.

Further investigations have cast doubt on this interpretation. Studies based on the use of radioactively labelled alpha-bungarotoxin (I^{125}-α-BuTx), a snake toxin which binds specifically and irreversibly to the ACh receptor (AChR), have shown a reduction in the number of functional AChR sites in myasthenia gravis (Fambrough, Drachman and Satyamurti, 1973; Green, Miledi, Perez de la Mora and Vincent, 1975*a*). This reduction could account for the physiological defect in neuromuscular transmission in myasthenia gravis without the need for postulating a primary presynaptic abnormality.

An auto-immune basis for myasthenia gravis proposed independently by Nastuk, Strauss and Osserman (1959) and Simpson (1960) has been increasingly supported by recent evidence. Antibodies to nicotinic AChRs have been detected in myasthenia gravis serum by a variety of *in vitro* methods and a transient disease has been produced in mice by passive transfer with human myasthenia gravis IgG (Toyka, Drachman, Griffin, Prestronk, Winkelstein, Fischbeck and Kao, 1977). The mechanism by which these antibodies affect neuromuscular transmission, however, is still in doubt.

We have investigated neuromuscular transmission in acquired myasthenia gravis by an *in vitro* study of myasthenic muscle taken from 20 patients who underwent thymectomy at the National Hospital between 1973 and 1976. Electrophysiological observations have been combined with studies of AChR function using I^{125}-αBuTx, and we relate these results to our previously published data on ACh content and release in the same muscle (Ito, Miledi, Molenaar, Vincent, Polak, van Gelder and Newsom Davis, 1976). Preliminary results have been reported elsewhere (Green *et al.*, 1975*a*; Ito, Miledi, Molenaar, Newsom Davis, Polak and Vincent, 1978).

METHODS

Clinical Material

Twenty patients with myasthenia gravis have been studied. All patients showed the typical clinical features of the disease and had shown a positive response to intravenous edrophonium (Tensilon). Clinical details are given in Table 1. There were 11 females and 9 males, whose ages ranged from 14 to 54 years. Most patients had mild or moderate generalized disease (Grade IIa and IIb respectively, Osserman and Genkins, 1972), but there were 4 with acute severe disease (Grade III) and 3 chronic severe cases (Grade IV). Seven cases had thymoma (in Patient 6, a thymoma had been removed eighteen months before the onset of myasthenia gravis; the muscle biopsy was obtained at mediastinal re-exploration carried out to exclude the presence of residual thymus tissue). Striated muscle antibody was strongly positive in one, moderately positive in 3, and weakly positive in 4 cases. Anti-AChR antibody (Ito *et al.*, 1978) was present in 13 of 14 patients tested (*see* Table 1).

Medication given over the period preceding operation is listed in Table 1. In most cases, no anticholinesterase treatment was given for ten hours before operation. In one patient, no anticholinesterase medication had been taken for four months pre-operatively, and in another the total pre-operative dose was three tablets of pyridostigmine (total 180 mg) taken over the period day 4 to day 2 pre-operatively. Four patients were receiving alternate day treatment with Prednisone at low dosage.

Control. Intercostal muscle was obtained from 13 control patients in the course of a thoracotomy. Nine of these subjects had carcinoma of the lung but none had clinical signs of neurological disease. Two patients were undergoing mitral valvotomy, in one surgery was being undertaken for achalasia of the cardia and in the remaining patient a neurofibroma was removed. Their ages and diagnoses are given in Table 2.

Muscle Biopsy

All patients gave informed consent to biopsy. In the patients with myasthenia gravis a segment of parasternal intercostal muscle from the third interspace was removed from origin to insertion before the sternum was split. In the control patients, external intercostal muscle was removed in a similar manner from the anterolateral aspect of the chest wall usually in the sixth interspace. The tissue was placed in Ringer solution at room temperature, bubbled with 5 per cent CO_2 in oxygen, and transferred at once to a laboratory.

Electrophysiology

The muscle bundles were examined by conventional electrophysiological techniques (Katz and Miledi, 1965). In many experiments neostigmine (10^{-7}–10^{-6} g/ml) was used to inhibit cholinesterase and increase the size of the miniature end-plate potentials.

For investigation of the effect of α-BuTx on neuromuscular transmission in control human muscle a small bundle of muscle fibres was dissected, together with its nerve supply, and kept in oxygenated

TABLE 1. CLINICAL DETAILS OF PATIENTS WITH MYASTHENIA GRAVIS

Patient	Sex	Age	Duration of symptoms (months)	Grade*	Treatment (mg/24 h)			Anti-AChR† antibody	Striated muscle antibody	Thymoma
					Neostigmine	Pyridostigmine	Prednisone			
1	F	27	6	IIB	210	60	0	++	±	No
2	F	25	18	IIA	0	30[1]	0	n.d.	++	Yes
3	F	18	36	IIB	75	120	0	n.d.	—	No
4	F	33	15	IIB	180	0	0	n.d.	±	No
5	F	19	1	IIB	150	0	0	n.d.	—	No
6	M	25	6	III	0	840	15	+	—	Yes
7	M	28	72	IV	0	600	0	+	—	No
8	M	27	4	IIB	0	600	0	++	—	No
9	M	18	18	IIB	45	450	25	+++	—	No
10	F	27	8	IIB	30	240	0	+	—	No
11	F	54	144	IV	60	300	10	n.d.	—	No
12	F	26	2	IIB	90	180	0	+++	+	Yes
13	M	18	3	III	120	600	0	±	—	No
14	M	54	27	IV	0	0[2]	10	++	±	Yes
15	F	36	24	IIB	45	360	0	+++	±	Yes
16	M	48	8	IIB	0	0[3]	0	n.d.	+	Yes
17	F	14	6	IIA	0	450[4]	0	++	+	No
18	M	26	3	III	0	300	0	+	—	No
19	F	38	3	III	0	600	40	+	—	No
20	M	47	34	IIB	0	240	0	+++	+	Yes

* IIA = mild generalized. IIB = moderate generalized. III = acute severe. IV = chronic severe. (Osserman and Genkins, 1972) † Moles α-BuTx binding sites precipitated/litre serum. ± = $< 5 \times 10^{-10}$. + = 5–50. ++ = 50–500. +++ = > 500. [1] Maximum daily dose for three weeks before operation. [2] No anticholinesterase medication for four months pre-operatively. [3] No anticholinesterase medication for twenty-four hours pre-operatively; total pre-operative anticholinesterase medication was 180 mg pyridostigmine given over pre-operative days 4 to 2. [4] No anticholinesterase medication for twenty-four hours pre-operatively.

Ringer solution at 34° C. One end of the bundle was fixed and the other attached to a tension transducer (RCA 5734). The nerve was lifted into a layer of liquid paraffin and placed on fine platinum electrodes for stimulation. In a separate experiment m.e.p.ps were recorded from control muscle during exposure to α-BuTx. In some experiments (6 patients with myasthenia gravis and 4 controls) ACh noise analysis was performed (Katz and Miledi, 1970, 1972).

Bungarotoxin Binding

α-Bungarotoxin was purified from the venom of Bungarus multicinctus (Taiwan and Miami Serpentarium) by ion-exchange chromatography and gel-filtration (D. Green and R. Miledi, unpublished) using a method similar to that of Chang and Lee (1963). The purified toxin was labelled radioactively with I^{125} (Vogel, Sytkowski and Nirenberg, 1972) using 100–500 μg of toxin and 2–5 mCi of Na I^{125}. The radioactive di-iodo toxin had a specific gravity of $10–50 \times 10^6$ cpm/μg when counted on the Packard automatic gamma counter 5220.

Incubation and washing. Bundles of fibres, unavoidably containing some damaged or cut fibres, were incubated in the labelled toxin in Krebs' Ringer at a concentration of 1 μg/ml for three to four hours. After incubation the muscle pieces were washed in oxygenated Ringer for one to two hours at room temperature before being pinned out on Silgard (Dow Corning Corporation) and left in a large volume of Ringer overnight in the refrigerator. In some experiments radioactivity in muscle bundles was counted in the gamma counter during washing in order to determine the rate of toxin loss during washout. Fixation was performed in 2 per cent glutaraldehyde in 70 per cent Ringer for two hours. Small groups of fibres or single fibres were then teased and laid on gelatinized glass slides for autoradiography. The rest of the bundles were stained for cholinesterase (Couteaux, 1955) and post-fixed in 2–5 per cent glutaraldehyde. Damaged or cut fibres were removed as far as possible and clean bundles containing between 20–50 fibres were examined under the dissecting microscope. A 2–3 mm segment containing all the end-plates was taken for determination of bound toxin by gamma counting. A similar segment devoid of end-plates ('non-end-plate segment') was also counted; 2–10 bundles were taken from each incubation.

Kinetics of toxin binding to human end-plates. The rate and degree of reversibility of toxin binding was investigated by taking similar sized bundles and incubating in the toxin for different periods, or fixing the tissue after different washing times.

Determination of number of fibres in each bundle and number of I^{125}-α-bungarotoxin binding sites per end-plate. The non-end-plate segment was fixed in osmium, dehydrated in alcohol and embedded in araldite. Thick sections (1 μ) were taken and stained with toluidine blue. The number of fibres in each bundle was then counted and in several patients the circumference of each fibre was determined by using a projection microscope and drawing around each fibre at a set enlargement of 1000. The circumference was measured with a map reader traced around the profiles.

The number of toxin binding sites per end-plate was determined by subtracting the non end-plate binding from the end-plate binding and dividing by the number of muscle fibres. The non end-plate binding per fibre was also determined and expressed as sites/mm/fibre.

Autoradiography. The gelatinized slides with attached fibres were coated with Ilford Gel emulsion L4 and left at 4° C for periods ranging from three days to three weeks depending on the specific activity of the toxin. Control and myasthenic fibres were almost always exposed simultaneously so that a direct comparison could be made between them. The slides were developed with Kodak D-19, mounted in DPX (Raymond A. Lamb) and examined with a Zeiss microscope.

Measurements of end-plates. After measuring the radioactivity of the end-plate containing segments, muscle fibres were teased in glycerol and examined with a microscope. The length of the cholinesterase stained end-plates was determined by counting the number of adjacent sarcomeres in order to avoid complications introduced by different degrees of shrinkage during fixation. Autoradiographed end-plates were measured in the same way.

RESULTS

Effects of α-bungarotoxin on Neuromuscular Transmission

The experiments using α-BuTx to quantify end-plate AChRs were started in 1973. At that time it was first necessary to ascertain that toxin blocked neuromuscular transmission in human muscle as in rat and frog by binding to the AChR (Miledi and Potter, 1971). This was established *in vitro* by examining the effects of the toxin on muscle twitch tension evoked by nerve stimulation, and on m.e.p.p. amplitudes. Fig. 1A shows the fall of twitch tension evoked by nerve stimulation after exposure to 1 μg/ml of α-BuTx in control intercostal muscle. There was progressive decline in twitch tension which began about six minutes after exposure to toxin and was complete at twenty minutes. No recovery occurred despite repeated washing in Ringer for one hour. Direct stimulation of the muscle caused a normal twitch.

The finding that α-BuTx progressively reduced the amplitude of m.e.p.ps (fig. 1B) without altering their frequency, and that normal action potentials could still be evoked by direct stimulation of muscle fibres after α-BuTx has reduced m.e.p.ps to undetectable levels, indicates that the block of neuromuscular transmission is due to blockage of AChRs. As in frog and rat muscle (Miledi and Potter, 1971) the rate of decrease of m.e.p.p. amplitude varied considerably at different end-plates (*see* fig. 1B).

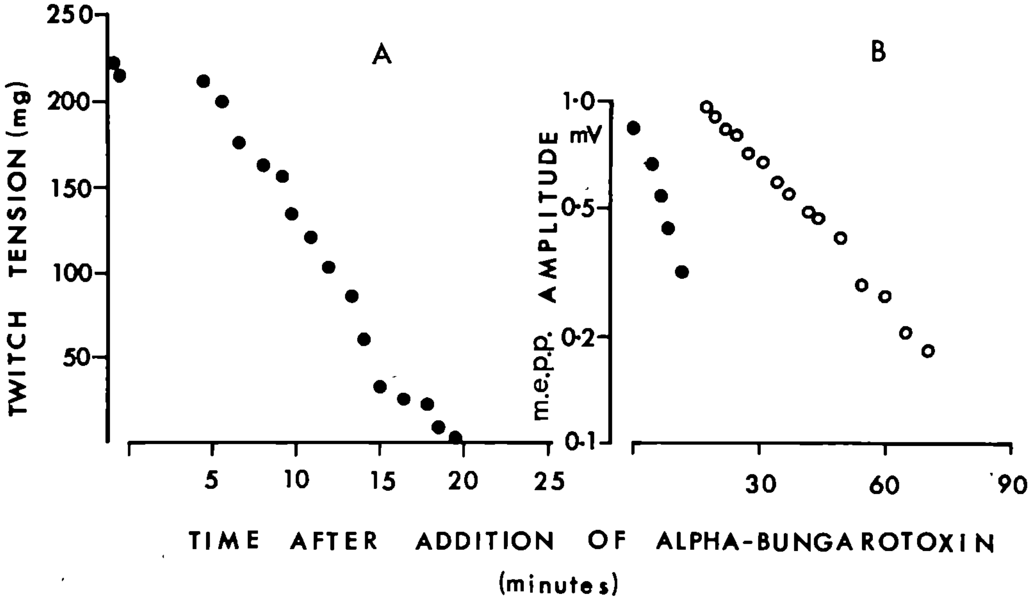


FIG. 1. The effect of α-BuTx on neuromuscular transmission in control human muscle. A, twitch tension: the points represent the mean response to three supramaximal stimuli at 1/s. Temperature 34° C. B, m e.p.p. amplitude: the filled circles represent values from one end-plate, the open circles from another. Resting potential 66–73 mV Temperature 25° C α-BuTx was added at time zero in each case.

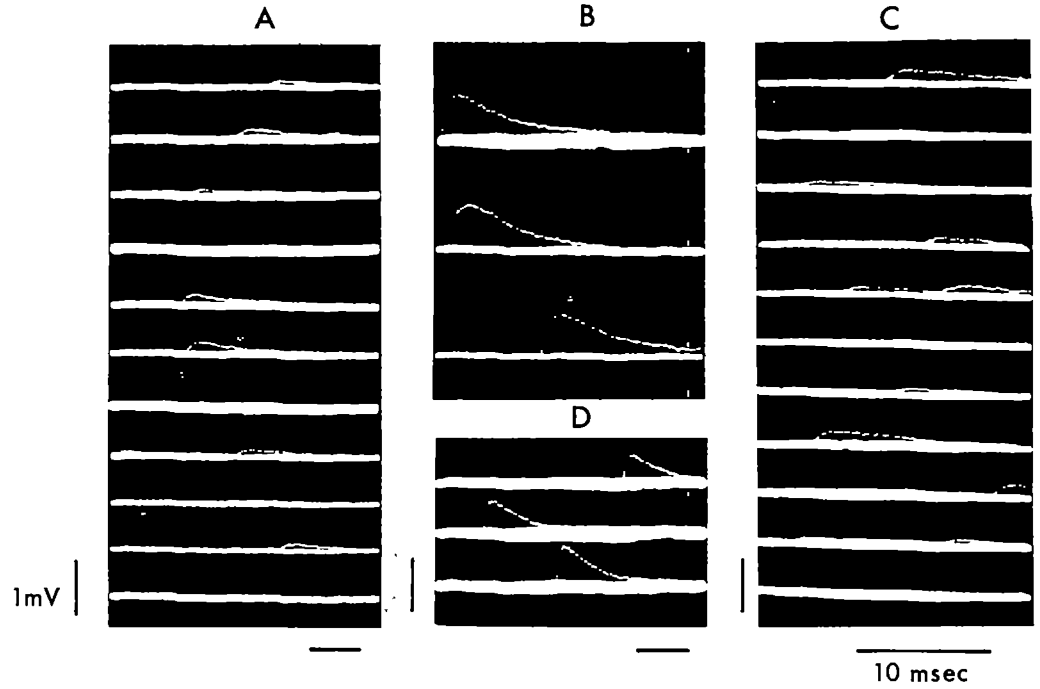


FIG. 2. Representative m.e.p.ps recorded from a control muscle (B), Case 10 (A) and Case 11 (C) in Ringer with 10^{-6} g/ml of neostigmine. Control m.e p.ps in the absence of neostigmine are shown in D.

TABLE 2. CLINICAL DETAILS AND EXPERIMENTAL DATA ON CONTROLS

Age	Diagnosis	*M.e.p.p. amplitude mV ± SD corrected to −80mV (no. fibres)* No Prostigmine	*Prostigmine 10^{-6} g/ml*	*α-BuTx binding sites per end-plate (× 10^7) ± s.e.m. (no observations)*	*Length of end-plates sarcomeres (~3μ) ± SD (no observations)*	*ACh content picomoles/g (mean of 2–4 determinations)*
53	Ca. lung			1 64±0 14 (2)	7·5±1 0 (7)	
62	,,			1 10±0 11 (11)	6·9±1 1 (8)	
62	,,			1 92±0 34 (5)		
44	Mitral valvotomy			1 76±0 16 (9)	6·7±0 9 (9)	
58	,,	0·70±0·19 (9)		1 87±0·20 (3)		
66	Ca. lung		1 03±0 22 (10)			245*
55	,,					120*
63	,,	0·70±0·09 (7)				168*
40	Achalasia	0·64±0·16 (3)	0 86±0·15 (3)	1 77±0·32 (9)	9·5±2 3 (38)	190*
63	Ca. lung		0·94±0·15 (4)	1·91±0·14 (5)		243†
65	,,		1 06±0·05 (3)	0 92±0 15 (5)	7·07±1 46 (30)	150†
57	,,			1·15±0·10 (5)	7·96±1 7 (24)	177†
61	Neurofibroma			1·65±0·48 (3)		

* Ito *et al* (1976). † Ito, Miledi and Molenaar (unpublished results)

Miniature End-plate Potential Amplitude

Examples of m.e.p.ps in control muscles are shown in fig. 2 and the mean values in individual control subjects are given in Table 2. In myasthenia gravis many m.e.p.ps are small and are lost in the noise of the recording system (figs. 2, 3) and prostigmine (10^{-7}–10^{-6} g/ml) was frequently used to enhance the potentials.

M.e.p.p. amplitudes in myasthenic end-plates showed a skew distribution (fig. 3A) in contrast to the normal distribution at control end-plates (fig. 3B). This indicates that many m.e.p.ps were lost in the noise of the recording system and helps to explain why the apparent rate of discharge of m.e.p.ps is lower in most myasthenia gravis end-plates. The addition of neostigmine had the expected effect of increasing the amplitude and time course of the m.e.p.ps (*see* figs. 2, 3 and Table 3) but even after neostigmine a skew amplitude distribution was still observed at many myasthenia gravis end-plates.

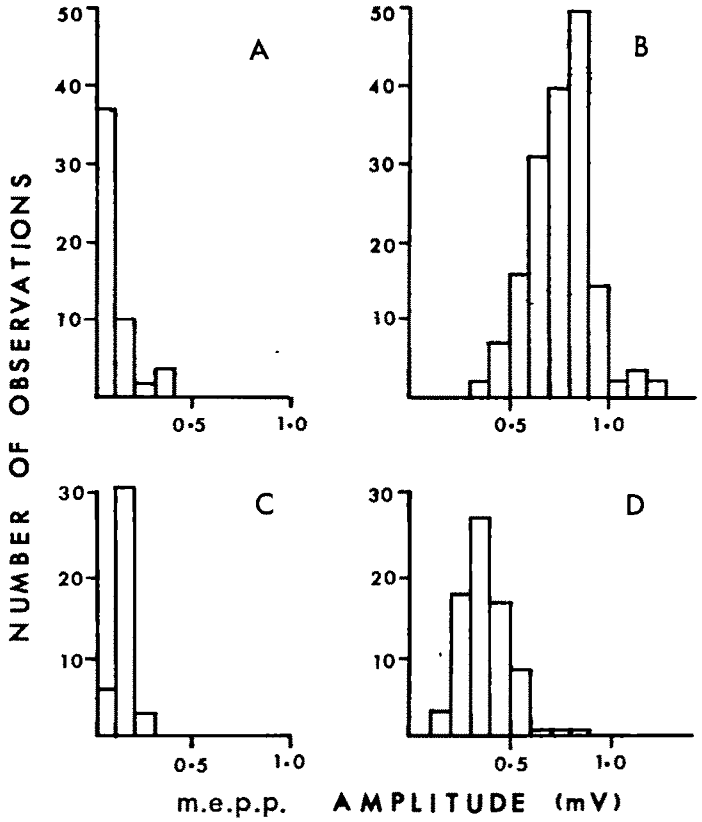


FIG 3. Histograms of m.e.p.p. amplitudes recorded from representative individual fibres: Case 5 (A) and a control (B) in normal Ringer; Case 13 (C) and Case 14 (D) in the presence of neostigmine 10^{-6} g/ml.

Average m.e.p.p. values from patients with myasthenia gravis are listed in Table 3. Since the resting potential of the muscle fibres was sometimes low because of damage, especially in the myasthenia gravis biopsies, the values given in Table 3 have been corrected to a resting potential of −80 mV. We found no obvious difference in the time course of the m.e.p.ps between control and myasthenic muscle either with or without added neostigmine.

TABLE 3. EXPERIMENTAL DATA IN MG PATIENTS

	M.e.p.p. amplitude mV ± SD corrected to −80 mV (no. fibres)		*α-BuTx binding sites per end-plate (× 10) ± s.e.m. (no. observations)*	*Length of end-plates sarcomeres (∼3μ) ± SD (no. observations)*	*ACh content picomoles/g (mean of 2–4 determinations)*
Patient	*No Prostigmine*	*Prostigmine 10^{-6} g/ml*			
1	0·2±0·13 (3)		0·58±0·10 (4)		
2			0·52±0·31 (5)	11·7±2·9 (14)	
3			0·96±0·13 (9)	17·0±8·3 (33)	
4			0·25±0·04 (3)	14·9±3·9 (9)	
5	0·27±0·16 (10)		0·28±0·03 (8)	10·5±1·3 (34)	
6			0·51±0·15 (5)		
7		0·59±0·13 (4)	0·70±0·20 (5)	16·92±2·25 (13)	719†
8		0·73±0·13 (14)*	2·39±0·23 (4)*	13·62±2·7 (10)	498†
9	0·26±0·1 (4)	0·37±0·12 (6)	0·64±0·18 (7)	15·9±5·8 (18)	360†
10		0·19±0·04 (5)	0·51±0·11 (8)	13·3±3·9 (26)	95†
11		0·26±0·10 (12)	0·61±0·22 (7)	9·9±1·7 (12)	335†
12			0·36±0·02 (3)	7·9±1·3 (34)	
13		0·23±0·06 (10)	0·23±0·21 (3)	15·2±5·8 (19)	284‡
14		0·44±0·16 (4)	0·79±0·13 (4)	13·3±3·9 (25)	293‡
15		0·33±0·08 (5)	0·20±0·14 (6)	15·7±5·6 (11)	709‡
16	0·17±0·01 (3)	0·24±0·03 (11)	0·19±0·10 (4)	8·4±1·6 (29)	279‡
17			0·45±0·13 (3)	11·2±2·6 (83)	
18		0·13±0·04 (5)	0·26±0·05 (7)	11·1±4·5 (45)	
19			0·76±0·14 (6)	10·17±3·55 (23)	
20		0·17±0·03 (3)	0·45±0·09 (6)	17·47±6·22 (35)	

* DFP 10^{-6} g/m... † Ito *et al.* (1976) ‡ P. C. Molenaar and R. L. Polak (unpublished results)

Acetylcholine Noise

The action of ACh at the neuromuscular junction is accompanied by fluctuation of membrane potential due to random variations in the number of ionic channels which, at any time, are open as a consequence of the combination of ACh with its receptor. Analysis of these fluctuations in potential provides us with an estimate of the amplitude and time-course of the elementary event underlying the action of ACh (Katz and Miledi, 1970, 1972). Similar studies on human muscle are important to decide whether the small size of the m.e.p.ps in myasthenic muscle is due to a reduction in the number of channels opened by a given dose of ACh, or to a decreased amplitude of the elementary event which results from the opening of an individual channel.

Experiments carried out several years ago in collaboration with Sir Bernard Katz showed that the amplitude of the elementary event induced by ACh in control muscles was 0·3–0·4 μV (at 25° C). Myasthenic end-plates were less sensitive to ACh, that is a larger dose of ACh was needed to depolarize the muscle fibres, but the amplitude and time-course of the elementary event was similar to that of control muscles. In myasthenia, as in normal muscle, the ACh-sensitivity was restricted to the end-plate region and its immediate surrounding.

I^{125}-Alpha-bungarotoxin Binding

Control and myasthenic muscle, although usually obtained on different days, were incubated in a similar preparation of radioactively-labelled toxin at 1 μg/ml. The use of a radioactive gamma counter made it possible to monitor the 'wash-out' of reversibly bound or loosely attached toxin during the washing period. The number of counts in a piece of incubated muscle dropped rapidly during the first three to five hours after incubation but after overnight washing the loss of radioactivity was much slower. The amount of radioactivity remaining, however, was a poor index of the specific 'end-plate' binding of toxin. There was an appreciable amount of binding, apparently irreversible, to the tendons and to the muscle fibres themselves, outside the end-plate region. Only after isolating the end-plate segment of each bundle of muscle fibres was it possible to assess the level of specific junctional binding.

After the bundles had been fixed and washed, the end-plates were localized by cholinesterase staining. The distribution of toxin binding along the length of a bundle of 30 fibres from a control patient is shown in fig. 4A where the bundle, 1·1 cm in length, was chopped into 1 mm segments from tendon to tendon. The segment containing the end-plates has a marked peak of radioactivity which is represented as binding sites per individual fibre. In fig. 4 (B, C) the distribution of sites along two different bundles of myasthenic fibres is shown; the extrajunctional or non end-plate binding is very similar to the control but the end-plate peaks are considerably reduced.

The specific binding of α-BuTx to the end-plate was estimated by subtracting the amount of toxin bound to an adjacent non end-plate segment of muscle from that of the end-plate region. The number of binding sites per end-plate was then obtained by dividing this value by the number of fibres. The average results from three to four hours' incubation and overnight washing for each subject are included in Tables 2 and 3.

The average number of binding sites for myasthenia gravis end-plates was considerably reduced compared to controls, the mean values for the two groups being $0{\cdot}49 \times 10^7$ SD $\pm$ 0·22 (n = 19) and $1{\cdot}57 \times 10^7 \pm 0{\cdot}34$ (n = 10) respectively. This difference was highly significant ($P < 0{\cdot}001$). (One myasthenia gravis result was excluded from these mean values. This biopsy was inadvertently placed in Ringer containing DFP 10^{-6} g/ml, and the binding proved to be higher than that of controls.) The histograms in fig. 5 reveal a symmetrical distribution for the number of toxin binding sites in control muscles (fig. 5B) but a skew distribution for myasthenia gravis muscles (fig. 5A) similar to that found in the m.e.p.p. amplitude histograms. In fact there were a few muscle bundles from patients with myasthenic gravis which showed less binding in the end-plate segment than in the non end-plate segment, and these values (which are negative since the non end-plate binding is subtracted from the end-plate binding, *see* Methods) have been included in the average values given above.

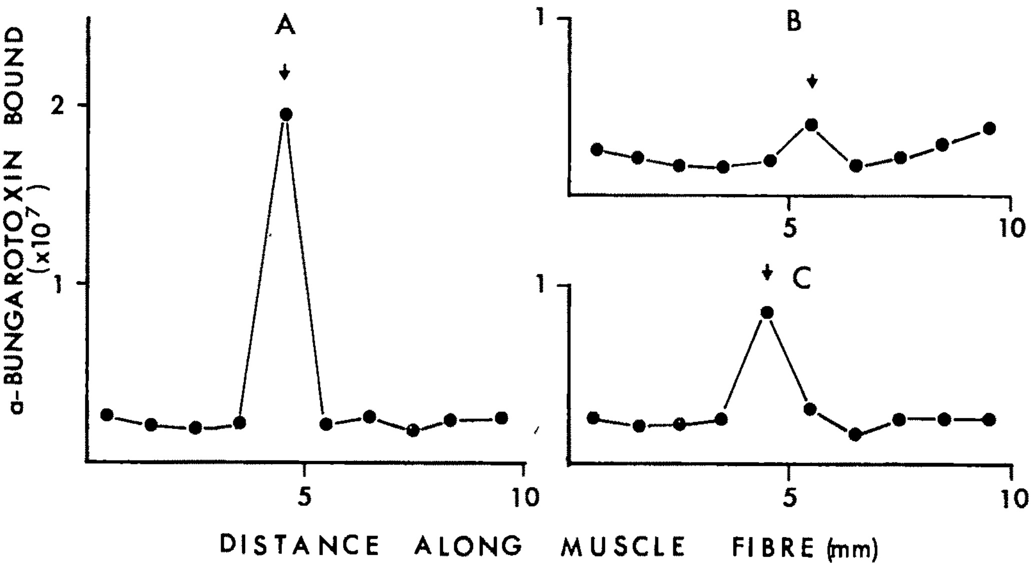


FIG 4. Distribution of α-BuTx binding sites along the length of muscle fibres from A, a control, B, Case 5 and C, Case 9. The segments which contained the end-plates are marked with an arrow. Results are expressed as mean α-BuTx binding sites/fibre in each segment.

In myasthenic muscle, there was a positive correlation between mean m.e.p.p. amplitude in neostigmine and α-BuTx binding (r = 0·71) significant at the 5 per cent level, that is, individuals with low α-BuTx binding tended to have smaller m.e.p.p. amplitudes than those with higher binding levels (fig. 6). There appeared, however, to be no clear relationship between the clinical state, and either the levels of α-BuTx binding or m.e.p.p. amplitudes.

Kinetics of α-BuTx Binding

The rate at which α-BuTx reduced m.e.p.p. amplitude (fig. 1) suggested that two hours at 1 μg/ml of α-BuTx should be more than sufficient to saturate the end-plate AChR binding sites. However, because of the small size of m.e.p.ps in

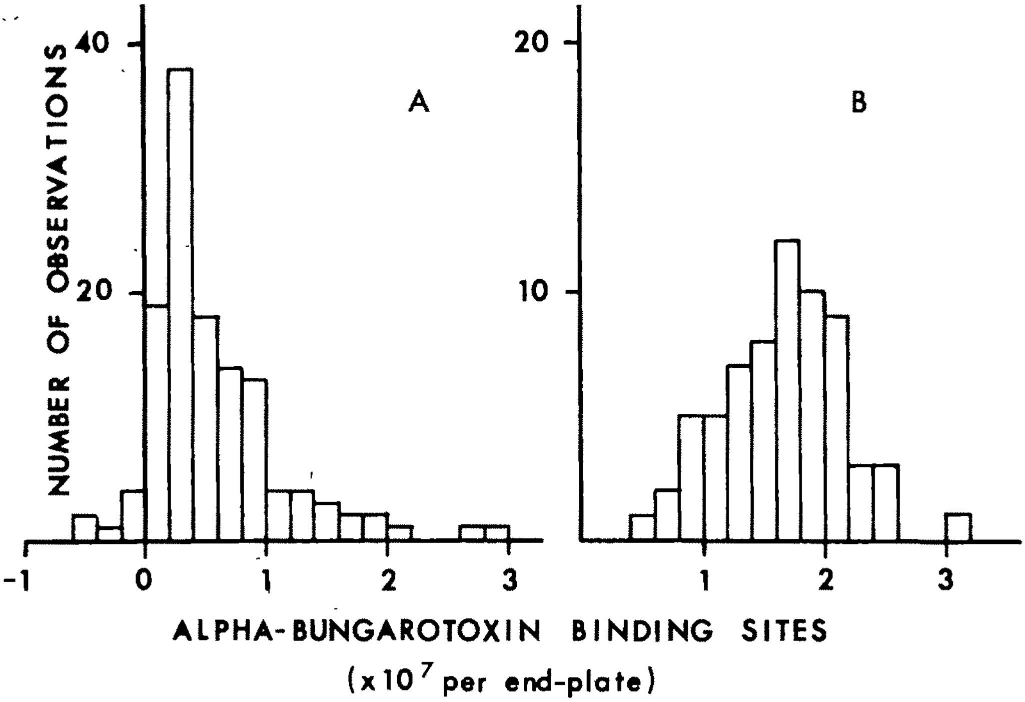


FIG. 5. Histograms of α-BuTx binding to end-plates from 20 patients with myasthenia gravis (A) and 10 controls (B) Binding to an adjacent segment devoid of end-plates has been subtracted.

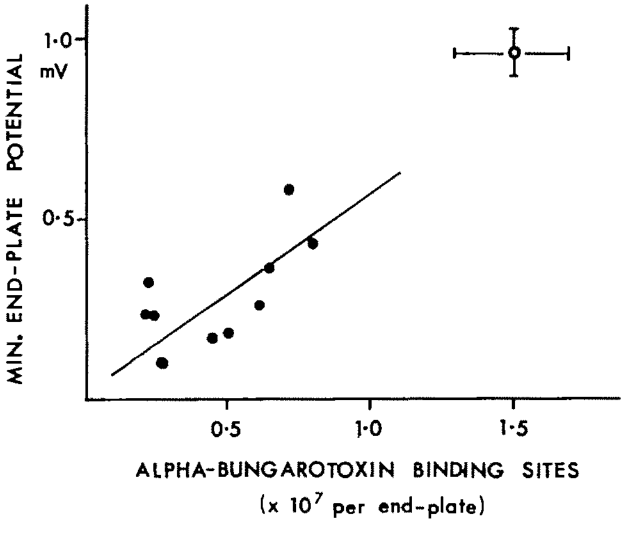


FIG. 6 Relationship between m.e.p.p. amplitude and α-BuTx binding in myasthenia gravis. The results represent the values obtained in the presence of neostigmine 10^{-6} g/ml and the regression line was calculated by the method of least squares The open circle and bars represent the mean plus standard deviations for the controls

myasthenic muscle it was impractical to assess the time-course of toxin blockage by recording m.e.p.ps. We therefore measured toxin binding in similar bundles of muscle incubated in the toxin for different periods of time, and in others which had been fixed before the usual overnight wash. The results for the different incubation times are shown in fig. 7. Control muscles had saturated by two to three hours and myasthenic muscle from four patients showed no increase in binding to the end-plate after three hours. These observations indicate that with the incubation used, the reduction in binding is not due to a slower rate of toxin binding to the myasthenic muscle.

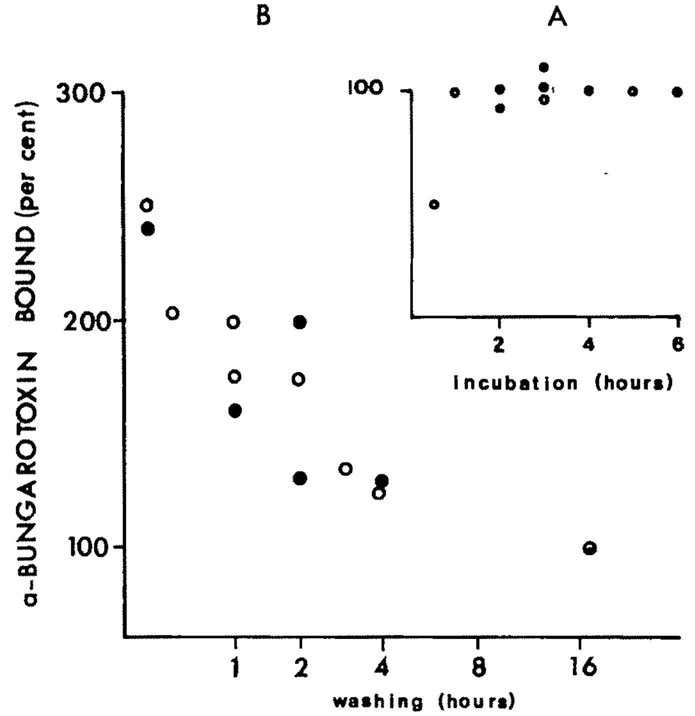


FIG 7. Kinetics of α-BuTx binding to the end-plate in myasthenia gravis (filled circles) and control muscle (open circles); end-plate binding after A, varying the incubation time, B, varying the washing time. Results are expressed as a percentage of values obtained with four hours incubation and sixteen hours wash.

The reversibility of the toxin binding was more difficult to estimate since shorter washing times meant higher extrajunctional binding and this made estimation of the specific end-plate binding less reliable, particularly in myasthenic muscle. In all biopsies, however, we found that the end-plate specific binding was higher if the washing time was restricted to 0–4 hours rather than continued overnight. Fig. 7

shows the results from 5 myasthenics and 5 controls. In both, the end-plate specific binding after a short washing period was about twice as high as that found after overnight washing, most of the loss of end-plate binding occurring in the first four hours. There did not appear to be any difference between control and myasthenic muscle as regards either the rate of loss or the reversibility of toxin binding. Preliminary studies show that approximately 70 per cent of the binding at short washout times is inhibited by carbachol (10^{-3} g/ml).

Extrajunctional α-bungarotoxin Binding and Acetylcholine Sensitivity

The extent of extrajunctional binding varies from muscle to muscle and was dependent on the age of the radioactive toxin and on the condition of the muscle fibres. The average non end-plate binding to myasthenic muscle was $0{\cdot}31 \pm 0{\cdot}04$ (SEM) $\times 10^7$ sites per mm fibre (17 muscles) and in the controls $0{\cdot}22 \pm 0{\cdot}04 \times 10^7$ (9 muscles). Assuming a simple cylindrical surface (of circumference 125 μ) this difference represents only about 7 sites per μ^2 of muscle fibre surface and is therefore approximately two orders of magnitude below the levels of extrajunctional toxin binding sites found in rat denervated muscle (Miledi and Potter, 1971; Fambrough, 1974). This accords with the lack of ACh sensitivity outside the end-plate region (*see above*). A few attempts were made to reduce the extrajunctional binding but there was no consistent change after incubating in the presence of either ACh, curare, albumin or sodium iodide. On the other hand, ACh, carbachol and curare inhibited the toxin binding at the end-plate by 60–80 per cent, so confirming the specificity of the binding.

Autoradiography and Cholinesterase Staining of End-plates

End-plates from patients with myasthenia gravis are frequently elongated or dystrophic (Cöers and Desmedt, 1959) and it was of interest to see how closely the toxin binding followed the cholinesterase staining. Some examples of autoradiograms and cholinesterase stained end-plates are shown in fig. 8 and histograms of the length of end-plates in fig. 9. The average cholinesterase-stained end-plate in myasthenia gravis (*see* Table 3) varied in length from the control values of about 8 sarcomeres (~ 3 μ/sarcomere) (Table 2) to about 17 sarcomeres, with lengths of 20 or more being found frequently in 3 patients (Cases 3, 13 and 20). Toxin binding sites followed these values closely (*see* fig. 9). Autoradiography shows that in controls (fig. 8) the toxin binding sites are almost entirely restricted to a small, more or less circular, patch 5–10 sarcomeres in length, but in the myasthenic muscles the toxin binding area was often elongated, and the density of autoradiographic grains much reduced (fig. 8). Nevertheless there were some end-plates where the distribution and density of binding was not grossly different from the controls although other end-plates from the same patients were obviously abnormal. In others the density of grains was reduced although the size of the end-plate was normal (fig. 8). The variation in density and distribution between

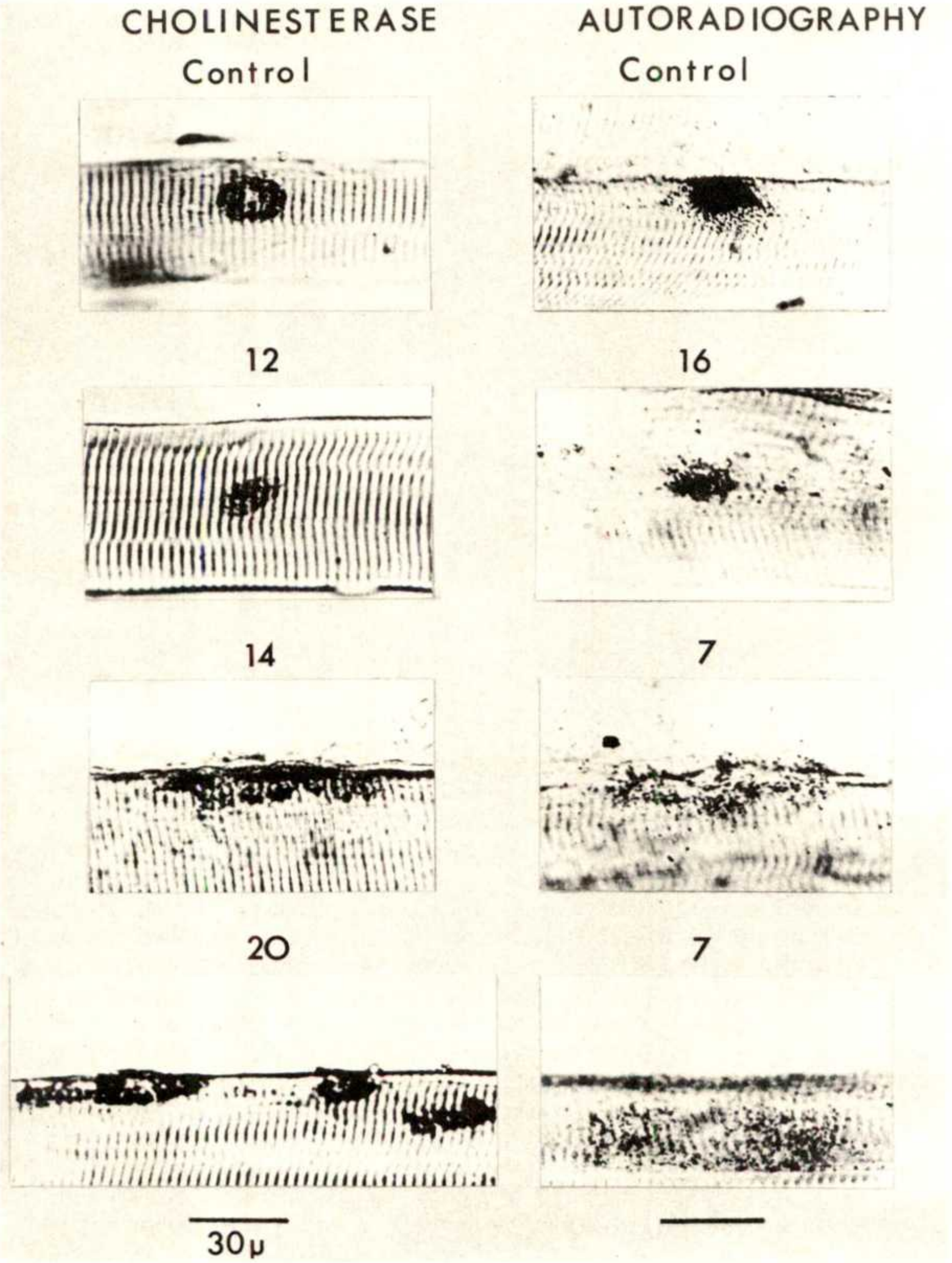


FIG. 8. Cholinesterase staining and autoradiography of myasthenic and control end-plates. Numerals refer to patients in Table 1.

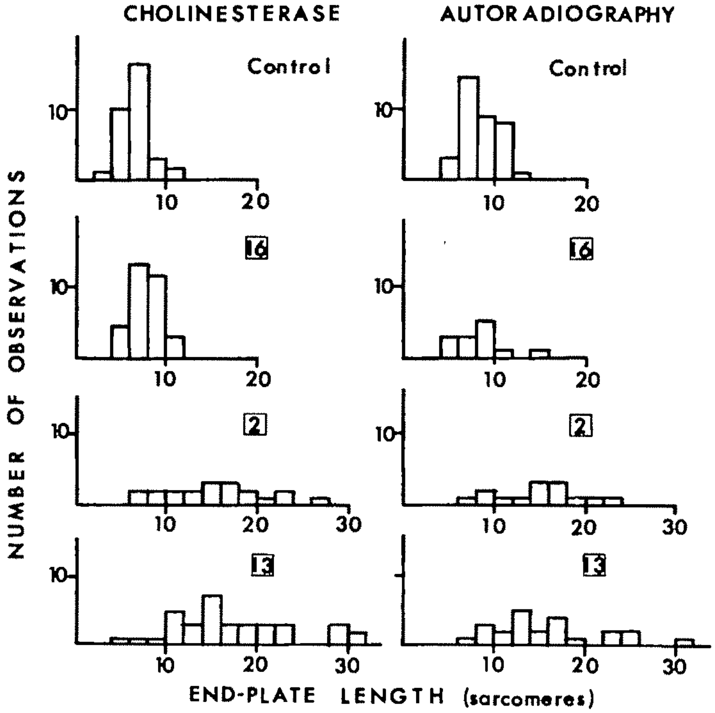


FIG. 9. Length of cholinesterase stained and autoradiographed end-plates of some myasthenic and control muscles Numbers in squares refer to patients in Table 1.

different end-plates from the same patients made statistical analysis difficult but preliminary observations confirm that the end-plate binding is higher after short washing periods.

Denervation in Myasthenia Gravis

A reported feature of myasthenic muscle is the presence of small angulated fibres found in cross-section (Engel, 1974), suggesting partial or chronic denervation. However, while counting muscle fibres from cross-sections of araldite-embedded bundles we found no clear evidence of angulated fibres, and measurement of the circumference of approximately 100 fibres from each of 7 controls and 6 myasthenics was made to confirm these observations. The results are shown in fig. 10. The distribution is very similar although individual average circumferences varied from 110–150 μm. In no case was there any evidence of a population of fibres with reduced circumference.

Tetrodotoxin blocks the action potential in human muscle as in other vertebrate skeletal muscle. This is illustrated in fig. 11 and preliminary experiments suggest that in myasthenia gravis the action potentials are still sensitive to TTX in contrast

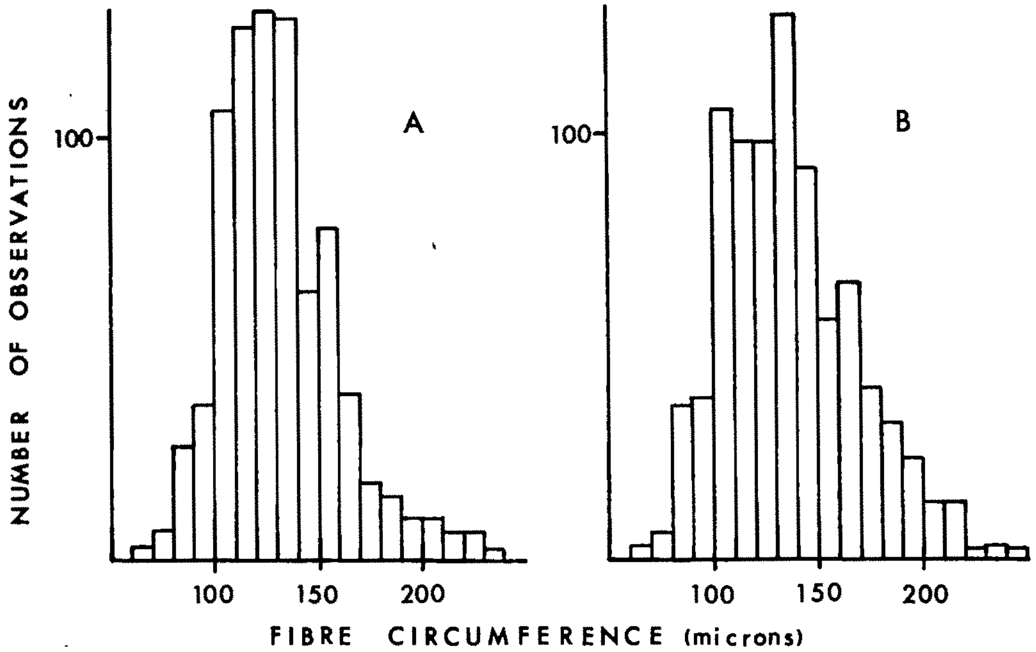


FIG. 10. Circumference of muscle fibres from A, 7 controls and B, 6 myasthenic muscles (Cases 3, 5, 7, 8, 12 and 14).

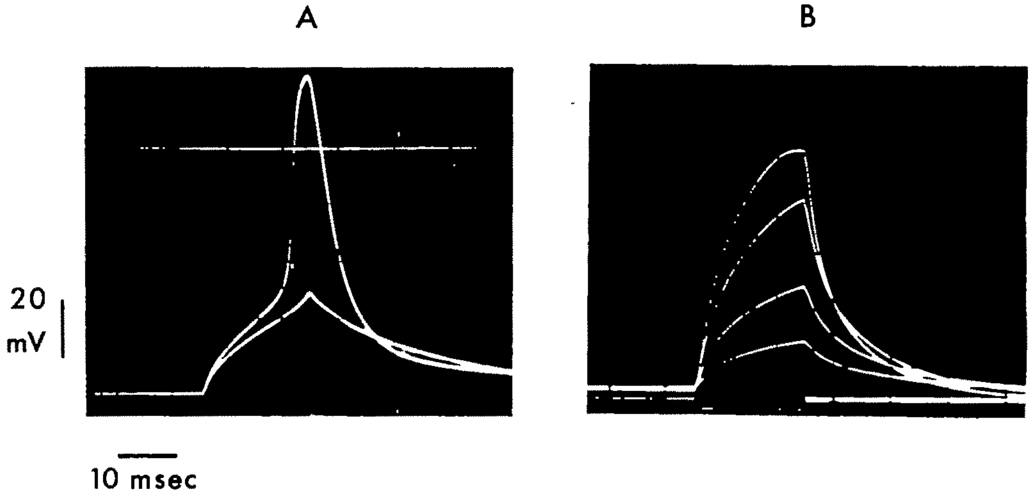


FIG. 11. Block of action potentials in control human muscle by tetrodotoxin. A, muscle fibre in normal Ringer, depolarized directly through a second microelectrode, showing one subthreshold and one threshold stimulation. B, muscle fibre depolarized to various levels after applying tetrodotoxin 10^{-6} g/ml Note the absence of action potentials.

to rat muscle fibres where action potentials become tetrodotoxin-resistant after denervation (Harris and Thesleff, 1971). These observations, together with the absence of abnormal extrajunctional toxin binding or ACh sensitivity, make the presence of denervation in our muscle biopsies very unlikely.

DISCUSSION

The effects of α-BuTx which we observed on human muscle demonstrate the usefulness of this snake toxin as a probe for AChRs at the human neuromuscular junction. The number of binding sites for radioactively-labelled toxin in human muscle is similar to that found in other species (Miledi and Potter, 1971; Barnard, Dolly, Porter and Albuquerque, 1975; Green *et al.*, 1975*a*). Although the small size of miniature end-plate potentials (m.e.p.ps) made it difficult to determine the efficacy of the toxin in blocking transmission in the myasthenic muscle, we found no obvious difference in the affinity of the labelled toxin for the receptor in myasthenia gravis. The reversibility of di-iodo-I^{125}-α-toxin binding which occurs in both control and myasthenic muscle during the first few hours after incubation has not previously been reported for an intact muscle preparation, but it may be related to that which Brockes and Hall (1975) found in solubilized and purified rat muscle extracts. Progressive acetylation of α-BuTx has been shown to reduce the affinity of the toxin derivative for the end-plate AChRs (Chang, Chen and Chuang, 1973*a*) and iodination of α-BuTx reduced the rate constant for toxin binding to AChRs at the frog neuromuscular junction (Green *et al.*, 1975*a*). It may be that di-iodo toxin binding to the human AChR is more reversible than binding of the native toxin. Whether this reversibility is accompanied by physiological recovery has yet to be ascertained.

The ACh sensitivity of myasthenic end-plates was found to be clearly less than controls (*see* Albuquerque, Rash, Mayer and Satterfield, 1976) and the voltage noise analysis indicates that the elementary potential event induced by the combination of ACh with the receptor is the same in control and myasthenic end-plates. This implies that with an elementary event amplitude of about 0·3 μV the miniature end-plate potentials are built up of the combined action of some 3000 elementary events in control muscle, and only 1000 or less in myasthenic end-plates. Most probably this difference arises from a difference in the number of available receptors because we found that the reduction in m.e.p.p. amplitude in myasthenia gravis is typically associated with a reduction in the number of α-BuTx binding sites in the same muscle, and that there is a significant positive correlation between the two variables. Moreover the regression line passes close to the mean values for our control patients. Thus the decrease in AChRs, as demonstrated by reduced α-BuTx binding, could fully account for the decreased effect of each quantum and the reduction in ACh sensitivity.

Quantitative electron microscopic studies have shown that the mean area of postsynaptic membrane per nerve terminal is reduced in myasthenia gravis (Santa, Engel and Lambert, 1972) and this might account for some of the reduction in toxin binding sites. In some of our patients, however, reduced m.e.p.ps and reduced α-BuTx binding have been associated with normal end-plate morphology (unpublished observations). Moreover, a recent study by Albuquerque *et al.* (1976) correlates electrophysiological findings with the morphological abnormalities. These authors also could not adequately account for the reduction in m.e.p.p. amplitude solely on the basis of morphological changes, since they found end-plates with small m.e.p.ps and reduced ACh sensitivity which appeared to be of normal structure.

It seems unlikely that an abnormal configuration of the AChR in myasthenia gravis could account for our findings because analysis of ACh 'noise' reveals no difference between myasthenic patients and controls and we found binding kinetics to be similar to those in healthy muscle. It thus appears probable that the defect in neuromuscular transmission in myasthenia gravis is related to a reduction in the number of AChRs available to ACh released from the nerve terminals.

Engel, Lindstrom, Lambert and Lennon (1977) have recently demonstrated a correlation between the length of postsynaptic membrane binding peroxidase-labelled α-BuTx and the amplitude of m.e.p.ps in four patients with myasthenia gravis. It is not clear from their results whether the total α-BuTx binding membrane is reduced since they measured the length of peroxidase-stained membranes in cross-section and did not quantify the total peroxidase-stained area. The reduction in α-BuTx binding which we have demonstrated therefore may be due to a reduction in the density of available AChRs or to a reduction in the area of AChR-containing membranes.

The cause of the elongated end-plates and ultrastructural changes which are so often encountered in myasthenia gravis is unknown although similar changes have been reported in rats treated for several months with anticholinesterases (Engel, Lambert and Santa, 1973; Schwartz, Sargeant and Swash, 1977). Reduced m.e.p.p. amplitudes and reduced bungarotoxin binding have also been found in rats treated for a short period with prostigmine (Chang, Chen and Chuang, 1973*b*). Unfortunately few studies of myasthenia gravis include more than one or two cases which have not received anticholinesterase treatment. In our experience of the two patients who received little or no anticholinesterase in the previous months, one had normal-looking end-plates and the other had moderately elongated ones. However, both had reduced toxin binding and small m.e.p.ps. One other patient had end-plates of normal size which might equally well be explained by the short duration of her disease, or of her anticholinesterase treatment. On the present evidence it seems impossible to determine whether elongation of the end-plate is secondary to long-term anticholinesterase treatment, or to the neuromuscular defect itself. Cöers (1975) has recently published evidence that these 'dysplastic' end-plates occur mainly in young female patients, and that the 'dystrophic' end-plates are found in older ones. Most of our patients would come into this lower age group.

An increase in the ACh content of myasthenic muscle found in 8/9 patients as compared with 8 controls is difficult to explain. The increased ACh could be either cytoplasmic or in the synaptic vesicles and may represent a secondary change related to the defect in neuromuscular transmission. It is unlikely that the increased ACh is in the muscle itself since 74 per cent of ACh in normal muscle is related to the nerve terminals (Miledi, Molenaar and Polak, 1977), but this point is difficult to exclude with fresh human muscle. The increase in ACh content of myasthenic muscle is probably not caused by anticholinesterase treatment since a slight increase was observed in one mild untreated case (Patient 16) while in 5 patients with congenital myasthenia gravis who were all on anticholinesterase treatment no increase was seen (Molenaar, Newsom-Davis and Vincent, unpublished results).

Extrajunctional α-BuTx binding sites have been found in small or angulated muscle fibres taken from patients with peripheral neuropathies or motor neuron disease which are associated with denervation (Ringel, Bender and Engel, 1976; Drachman and Fambrough, 1976). Moreover long-term administration of α-BuTx or curare to block neuromuscular transmission has been shown to result in the appearance of extrajunctional ACh sensitivity in rat muscle (Berg and Hall, 1975). The absence of denervation features in myasthenic muscle is therefore surprising since there were many end-plates which were functionally denervated at the time of the study, that is, there was no action potential in response to nerve stimulation. The presence of extrajunctional AChRs in myasthenia gravis might be concealed by the presence of a serum blocking factor (*see* Ringel *et al.*, 1976) but the lack of a population of abnormally small fibres in our biopsies argues against this.

Immune Basis of Myasthenia Gravis

What is the nature of the factor responsible for the reduction in functional AChRs? Evidence that 'thymopoietin' (Goldstein and Schlesinger, 1975) might be the causative factor underlying our observations is not convincing. Goldstein and Whittingham (1966) described a disorder electromyographically resembling myasthenia gravis in the experimental animal following induction of an auto-immune thymitis, and subsequently Goldstein and Schlesinger presented evidence for a thymic humoral agent of low molecular weight (thymopoietin) as the active factor. The animals did not show any clinical signs of myasthenia, however, and several other groups have been unable to reproduce the experiments (e.g. Vetters, Simpson and Folkarde, 1969; Jones, Brennan and McLeod, 1971).

An autoimmune model of myasthenia gravis can be induced in animals (Patrick and Lindstrom, 1973; Heilbronn, Mattsson, Stälberg and Hilton-Brown, 1975; Green, *et al.*, 1975*b*; Lennon, Lindstrom and Seybold, 1975) including primates (Tarrab-Hazdai, Aharanov, Silman and Fuchs, 1975) by injection of purified AChR. Application of serum from immunized rabbits to neuromuscular preparations causes reduced m.e.p.p. amplitude (Green *et al.*, 1975*b*), diminished ACh sensitivity (Bevan, Heinemann, Lennon and Lindstrom, 1976) and neuromuscular block (Berti, Clementi, Conti-Tronconi and Folco, 1976); these changes are very similar to the findings in the human disease. In rats morphological changes occur which are also very similar to those described for myasthenia gravis (Engel, Tsujihata, Lambert and Lindstrom, 1976).

An immune basis for myasthenia gravis, as independently suggested by Nastuk, Strauss and Osserman (1959) and Simpson (1960), has been receiving increasing support. Serum from myasthenic patients can interfere with α-BuTx bindings to the AChR from denervated rat muscle (Almon, Andrew and Appel, 1974) and at the human neuromuscular junction (Bender, Ringel, Engel, Daniels and Vogel, 1975), and circulating antibody to AChRs has been demonstrated in myasthenia gravis (Aharanov, Abramsky, Tarrab-Hazdai and Fuchs, 1975; Lindstrom, Seybold, Lennon, Whittingham and Duane, 1976; Ito *et al.*, 1978). Serum from myasthenic patients can passively transfer to mice a disorder of neuromuscular transmission which is electrophysiologically similar to myasthenia gravis, and in which binding of labelled α-BuTx to AChR is reduced (Toyka, Drachman, Griffin, Pestronk, Winkelstein, Fischbeck and Kao, 1977). In a few instances we observed reduction in m.e.p.p. amplitudes in healthy human muscle *in vitro* in the presence of myasthenia gravis serum. More work is needed to assess the significance of these preliminary observations.

Evidence that a humoral factor in plasma plays a primary role in the disorder of neuromuscular transmission is provided by the unequivocal clinical remission which follows plasma exchange in acquired myasthenia gravis (Pinching, Peters and Newsom Davis, 1976). Studies on the effects of thoracic duct drainage in myasthenia gravis, which also causes clinical improvement, suggest that the humoral factor is in the gamma globulin fraction (Bergström, Franksson, Matell and von Reis, 1973; Lefvert and Bergström, 1976). Recently IgG and complement C_3 have been demonstrated at the end-plate in myasthenia gravis by immunohistochemistry (Engel, Lambert and Howard, 1977) and a marked inverse relation has been shown between anti-AChR antibody levels and clinical state during and after plasma exchange (Newsom Davis, Pinching, Vincent and Wilson, 1978).

In conclusion, the principal abnormality in myasthenia gravis is postsynaptic rather than presynaptic and is characterized by a reduced number of functioning AChRs at the myasthenic neuromuscular junction. The reduction in the number of AChRs probably reflects a genuine decrease in density of the receptors in the postsynaptic membrane but morphological changes could also contribute to the reduction. An autoimmune destructive process involving anti-AChR antibody and C_3 occurs at the postsynaptic membrane (Engel, Lambert and Howard, 1977) and myasthenia gravis serum can increase AChR degradation of culture in muscle tissue (Anwyl, Appel and Narahashi, 1977; Appel, Anwyl, McAdams and Elias, 1977; Bevan, Kullberg and Heinemann, 1977; Kao and Drachman, 1977). The extent to which the disturbance of neuromuscular transmission is caused by pharmacological blocks of AChRs, destruction of the AChR-containing membrane or increase in AChR degradation is still not clear. It seems likely that all three mechanisms may play a part, perhaps at different stages of the disease.

SUMMARY

In studies of intercostal muscle taken at biopsy in 20 patients with myasthenia gravis, we have demonstrated a reduced number of functioning acetylcholine receptors compared to control muscle, and have further shown that the number of receptors is positively correlated with the mean amplitude of the miniature end-plate potentials. These findings indicate the presence of a postsynaptic defect in myasthenia gravis that is adequate to account for the disorder of neuromuscular transmission.

ACKNOWLEDGEMENTS

We would like to thank Mr. M. F. Sturridge, Mr. J. R. Belcher and Dr. L. Loh for help in obtaining the biopsies, and Mrs. B. Craine and Miss P. Jacobs for performing the autoradiography. We are grateful to the physicians at the National Hospital for Nervous Diseases for allowing us to study patients under their care. This work was supported by the Medical Research Council and by a Fellowship (to Y.I.) from the Wellcome Trust. Reprint requests to J. Newsom-Davis, Department of Neurological Science, Royal Free Hospital, Pond Street, London NW3 2QG.

REFERENCES

AHARANOV, A., ABRAMSKY, O., TARRAB-HAZDAI, R. and FUCHS, S. (1975) Humoral antibodies to acetylcholine receptor in patients with myasthenia gravis. *Lancet*, **ii**, 340–342.

ALBUQUERQUE, E. X., RASH, J. E., MAYER, R. F. and SATTERFIELD, J. R. (1976) An electrophysiological and morphological study of the neuromuscular junction in patients with myasthenia gravis. *Experimental Neurology*, **51**, 536–563.

ALMON, R. R., ANDREWS, C. G. and APPEL, S. H. (1974) Serum globulin in myasthenia gravis: inhibition of α-bungarotoxin binding to acetylcholine receptors. *Science*, **186**, 55–57.

ANWYL, R., APPEL, S. H. and NARAHASHI, T. (1977) Myasthenia gravis serum reduces acetylcholine sensitivity in cultured rat myotubes. *Nature, London*, **267**, 262–263.

APPEL, S. H., ANWYL, R., MCADAMS, M. W. and ELIAS, S. (1977) Accelerated degradation of acetylcholine receptor from cultured rat myotubes with myasthenia gravis sera and globulins. *Proceedings of the National Academy of Sciences of the United States of America*, **74**, 2130–2134.

BARNARD, E. A., DOLLY, J. O., PORTER, C. W. and ALBUQUERQUE, E. X. (1975) The acetylcholine receptor and the ionic conductance modulation system of skeletal muscle. *Experimental Neurology*, **48**, 1–28.

BENDER, A. N., RINGEL, S. P., ENGEL, W. K., DANIELS, M. P. and VOGEL, Z. (1975) Myasthenia gravis: a serum factor blocking acetylcholine receptors of the human neuromuscular junction *Lancet*, **i**, 607–609.

BERG, D. K. and HALL, Z. W. (1975) Increased extrajunctional acetylcholine sensitivity produced by chronic postsynaptic neuromuscular blockade. *Journal of Physiology, London*, **244**, 659–676.

BERGSTRÖM, K., FRANKSSON, C., MATELL, G. and VON REIS, G. (1973) The effects of thoracic duct lymph drainage in myasthenia gravis. *European Neurology*, **9**, 157-167.

BERTI, F., CLEMENTI, F., CONTI-TRONCONI, B. and FOLCO, G. C. (1976) A cholinoceptor antiserum; its pharmacological properties. *British Journal of Pharmacology and Chemotherapy*, **57**, 17-22.

BEVAN, S., HEINEMANN, S., LENNON, V. A. and LINDSTROM, J. (1976) Reduced muscle acetylcholine sensitivity in rats immunized with acetylcholine receptor. *Nature, London*, **260**, 438-439.

—— KULLBERG, R. W. and HEINEMANN, S. F. (1977) Human myasthenic sera reduce acetylcholine sensitivity of human muscle cells in tissue culture. *Nature, London*, **267**, 263-265.

BROCKES, J. P. and HALL, Z. W. (1975) Acetylcholine receptors in normal and denervated rat diaphragm. 1. Purification and interaction with 125I α-Bungarotoxin. *Biochemistry*, **14**, 2092-2099.

CHANG, C. C., CHEN, T. F. and CHUANG, S.-T. (1973*a*) N, O-di and N, N, O-tri (3H) acetyl-bungarotoxin as specific labelling agents of cholinergic receptors. *British Journal of Pharmacology and Chemotherapy*, **47**, 147-150.

—— —— —— (1973*b*) Influence of chronic neostigmine treatment on the number of acetylcholine receptors and the release of acetylcholine from the rat diaphragm. *Journal of Physiology*, **230**, 613-618.

—— and LEE, C. Y. (1963) Isolation of neurotoxins from the venom of Bungarus multicinctus and their modes of neuromuscular blocking action. *Archives Internationales de Pharmacodynamie et de Therapie*, **144**, 241-257.

CÖERS, C. (1975) Motor innervation of myasthenic muscles related to age. *Lancet*, **ii**, 55.

—— and DESMEDT, J. E. (1959) Mise en evidence d'une malformation characteristique de la jonction neuromusculaire dans la myasthenie. *Acta Neurologica et Psychiatrica Belgica*, **59**, 539-561.

COUTEAUX, R. (1955) Localisation of cholinesterases at the neuromuscular junction. *International Review of Cytology*, **4**, 335-375.

DRACHMAN, D. B. and FAMBROUGH, D. M. (1976) Are muscle fibres denervated in myotonic dystrophy? *Archives of Neurology*, **33**, 485-488.

ELMQVIST, D., HOFMANN, W. W., KUGELBERG, J. and QUASTEL, D. M. J. (1964) An electrophysiological investigation of neuromuscular transmission in myasthenia gravis. *Journal of Physiology*, **174**, 417-434.

ENGEL, A. G., LAMBERT, E. H. and HOWARD, F. M. (1977) Immune complexes (IgG and C3) at the motor end-plate in myasthenia gravis. Ultrastructural and light microscopic localization and electrophysiologic correlations. *Mayo Clinic Proceedings*, **52**, 267-280.

—— —— and SANTA, T. (1973) Study of long-term anticholinesterase therapy. Effects on neuromuscular transmission and on motor end-plate fine structure. *Neurology, Minneapolis*, **23**, 1273-1281.

—— LINDSTROM, J. M., LAMBERT, E. H. and LENNON, V. A. (1977) Ultrastructural localization of the acetylcholine receptor in myasthenia gravis and in its experimental autoimmune model. *Neurology, Minneapolis*, **27**, 307-315.

—— TSUJIHATA, M., LAMBERT, E. H., LINDSTROM, J. M. and LENNON, V. A. (1976) Experimental autoimmune myasthenia gravis: A sequential and quantitative study of the neuromuscular junction ultrastructure and electrophysiologic correlations. *Journal of Neuropathology and Experimental Neurology*, **35**, 569-587.

ENGEL, W. K. (1974) Myasthenia gravis. *Annals of Internal Medicine*, **81**, 225–246.

FAMBROUGH, D. M. (1974) Acetylcholine receptors: Revised estimates of extrajunctional receptor density in denervated rat diaphragm. *Journal of General Physiology*, **64**, 468–472.

—— DRACHMAN, D. B. and SATYAMURTI, S. (1973) Neuromuscular junction in myasthenia gravis. Decreased acetylcholine receptors. *Science*, **182**, 293–295.

GOLDSTEIN, G. and SCHLESINGER, D. H. (1975) Thymopoietin and myasthenia gravis: neostigmine-responsive neuromuscular block produced in mice by a synthetic peptide fragment of thymopoietin. *Lancet*, **ii**, 256–259.

—— and WHITTINGHAM, S. (1966) Experimental autoimmune thymitis: an animal model of human myasthenia gravis. *Lancet*, **ii**, 315–318.

GREEN, D. P. L., MILEDI, R., PEREZ DE LA MORA, M. and VINCENT, A. (1975*a*) Acetylcholine receptors. *Philosophical Transactions of the Royal Society, B*, **270**, 551–559.

—— —— and VINCENT, A. (1975*b*) Neuromuscular transmission after immunisation against acetylcholine receptors. *Proceedings of the Royal Society, B*, **189**, 57–68.

HARRIS, J. B. and THESLEFF, S. (1971) Studies of tetrodotoxin resistant action potentials in denervated skeletal muscle. *Acta Physiologica Scandinavica*, **83**, 382–388.

HEILBRONN, E., MATTSSON, C., STÅLBERG, E and HILTON-BROWN, P. (1975) Neurophysiological signs of myasthenia in rabbits after receptor antibody development. *Journal of Neurological Sciences*, **24**, 59–64.

ITO, Y., MILEDI, R., MOLENAAR, P. C., VINCENT, A., POLAK, R. L., VAN GELDER, M. and NEWSOM DAVIS, J. (1976) Acetylcholine in human muscle. *Proceedings of the Royal Society, B*, **192**, 475–480.

—— —— —— NEWSOM DAVIS, J., POLAK, R. L. and VINCENT, A. (1978) Neuromuscular transmission in myasthenia gravis and the significance of anti-acetylcholine receptor antibodies. In: *Biochemistry of Myasthenia Gravis and Muscular Dystrophy*. Edited by R. Marchbanks and G. Lunt. New York and London: Academic Press.

JONES, S. F., BRENNAN, J. L. and MCLEOD, J. G. (1971) An investigation of experimental myasthenia gravis. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 399–403.

KAO, I. and DRACHMAN, D. B. (1977) Myasthenic immunoglobulin accelerates acetylcholine receptor degradation. *Science*, **196**, 527–529.

KATZ, B. and MILEDI, R. (1965) Propagation of electric activity in motor nerve terminals *Proceedings of the Royal Society, B*, **161**, 453–482.

—— —— (1970) Membrane noise produced by acetylcholine. *Nature, London*, **226**, 962–963.

—— —— (1972) The statistical nature of the acetylcholine potential and its molecular components. *Journal of Physiology*, **224**, 665–699.

LEFVERT, A. K. and BERGSTRÖM, K. (1976) Effect of lymph IgG from patients with myasthenia gravis on cholinergic receptors. *European Journal of Clinical Investigation*, **6**, 334.

LENNON, V. A., LINDSTROM, J. M. and SEYBOLD, M. E. (1975) Experimental autoimmune myasthenia: A model of myasthenia gravis in rats and guinea pigs. *Journal of Experimental Medicine*, **141**, 1365–1375.

LINDSTROM, J. M., SEYBOLD, M. E., LENNON, V. A., WHITTINGHAM, S. and DUANE, D. D. (1976) Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. *Neurology, Minneapolis*, **26**, 1054–1059.

MILEDI, R., MOLENAAR, P. C. and POLAK, R. L. (1977) An analysis of acetylcholine in frog muscle by mass fragmentography. *Proceedings of the Royal Society, B*, **197**, 285–297.

—— and POTTER, L. T. (1971) Acetylcholine receptors in muscle fibres. *Nature, London*, **233**, 599–603.

NASTUK, W L., STRAUSS, A. J. L. and OSSERMAN, K. E. (1959) Search for a neuromuscular blocking agent in the blood of patients with myasthenia gravis. *American Journal of Medicine*, **26**, 394–409.

NEWSOM-DAVIS, J., PINCHING, A. J., VINCENT, A. and WILSON, S. G. (1978) Function of circulating antibody to acetylcholine receptor in myasthenia gravis: investigation by plasma exchange. *Neurology, Minneapolis*, **28**, 266–272.

OSSERMAN, K. E. and GENKINS, G. (1972) Studies in myasthenia gravis: review of twenty-year experience in over 1200 patients. *The Mount Sinai Journal of Medicine*, **38**, 497–537.

PATRICK, J. and LINDSTROM, J. M. (1973) Autoimmune response to acetylcholine receptor. *Science*, **180**, 871–872.

PINCHING, A. J., PETERS, D. K. and NEWSOM DAVIS, J. (1976) Remission of myasthenia gravis following plasma-exchange. *Lancet*, **ii**, 1373–1376.

RINGEL, S. P., BENDER, A. N. and ENGEL, W. K. (1976) Extrajunctional acetylcholine receptors: alterations in human and experimental neuromuscular diseases. *Archives of Neurology*, **33**, 751–758.

SANTA, S., ENGEL, A. G. and LAMBERT, E. H. (1972) Histometric study of neuromuscular junction ultrastructure 1. Myasthenia gravis. *Neurology, Minneapolis*, **22**, 71–82.

SCHWARTZ, M. S., SARGEANT, M. K. and SWASH, M. (1977) Neostigmine-induced end-plate proliferation in the rat. A study using supra-vital methylene blue. *Neurology, Minneapolis*, **27**, 289–293

SIMPSON, J. A. (1960) Myasthenia gravis. A new hypothesis. *Scottish Medical Journal*, **5**, 419–436.

TARRAB-HAZDAI, R., AHARANOV, A., SILMAN, I. and FUCHS, S. (1975) Experimental autoimmune myasthenia induced in monkeys by purified acetylcholine receptor. *Nature, London*, **256**, 128–130.

TOYKA, K. V., DRACHMAN, D. B., GRIFFIN, D. E., PESTRONK, A., WINKELSTEIN, J. A., FISCHBECK, K. H. and KAO, I. (1977) Myasthenia gravis. Study of humoral immune mechanism by passive transfer to mice. *New England Journal of Medicine*, **296**, 125–131.

VETTERS, J., SIMPSON, J. A. and FOLKARDE, A. (1969) Experimental myasthenia gravis. *Lancet*, **ii**, 28–31.

VOGEL, Z., SYTKOWSKI, A. J. and NIRENBERG, M. W. (1972) Acetylcholine receptors of muscle grown *in vitro*. *Proceedings of the National Academy of Sciences, USA*, **69**, 3180–3184.

(*Received December 22, 1977*)

Brain (1978), **101**, 369-379

NOTICES OF RECENT PUBLICATIONS

The Basal Ganglia. Edited by MELVIN D. YAHR. Association for Research in Nervous and Mental Disease. Vol. 55. 1976. Pp. 500. Price $42.00.

'The ganglia situated at the base of the brain, still to a large extent retained the characteristic of all basements, i.e. darkness'. So wrote Kinnier Wilson in 1925 after a decade in which he had attempted by experiment to reproduce the symptoms of the disease which bears his name. His own meticulous correlation of clinical and pathological observations had elucidated the connection between degeneration in the basal ganglia and the neurological manifestations of hepatolenticular degeneration. But he achieved no further illumination of the functions of the basal ganglia using accurately positioned and delineated lesions in animals. One can sympathize with his feelings of frustration and disappointment

Sadly things do not seem to have improved all that much to this day A recent volume from the Association for Research in Nervous and Mental Disease details much of what is now known about the basal ganglia. But in the intervening forty-one years, despite great advances in treatment of many of the diseases associated with these nuclei, and corresponding advances in understanding their neuropharmacology, one is still left with a rather nebulous impression of what they actually do. The lack of a final chapter entitled, for example, 'Summary and Conclusions—a Synthesis of Basal Ganglia Function' is symptomatic of the unsatisfactory state of our understanding. Presumably nobody felt confident enough at the meeting which this volume reports to embark on the explanations which might have lightened the darkness of Wilson's basement.

The classic methods of neurology which have yielded so much in other areas have until recently been of very little use in the case of the basal ganglia. The impetus to carry out experiments in the nervous system usually starts at the bedside with the need to understand neurological disease Nature has been remarkably prolific with her own experiments in these regions. One is always amazed at the variety of ways in which the basal ganglia can be affected, from the excess copper of Wilson's disease to the deposition of blood pigments in Kernicterus; through the long-term effects of encephalitis lethargica and the congenital deficiency of GABA in Huntingdon's chorea to the accelerated ageing leading to deficiency of dopamine in Parkinson's disease; from the, as yet undisclosed, pathology of the dystonias, to the extreme sensitivity of the basal ganglia to drugs. They seem to be especially delicate. This volume describes the diseases and current approaches to their treatment; but does not attempt any explanation for this peculiar vulnerability, or of the symptoms caused.

In thirteen chapters devoted to clinical aspects of basal ganglia disease there is very little discussion of the basic problems besetting analysis of their function, which were so clearly outlined in J. Purdon Martin's classic *The Basal Ganglia and Posture* published eight years previously. The diagnostic triad of symptoms in basal ganglia disorders, namely, involuntary movements, rigidity, and bradykinesia, is associated with widespread lesions of the corpus striatum, globus pallidus, subthalamic nucleus, substantia nigra, red nucleus and many structures in between. Unfortunately nature does not make neat lesions which respect anatomists' boundaries, so it has proved difficult to associate particular symptoms with particular regions. Though it is now almost an article of the neuroscientist's faith, that anatomical boundaries localize different functions of the nervous system, perhaps one should anyway bear in mind that there is no *a priori* justification for this. Kinnier Wilson's final view was that there is no localization of function whatsoever within the basal ganglia. This nihilism is echoed today by the 'holists' of brain science.

Small localized lesions actually very rarely do give rise to obvious symptoms, the fact which depressed Kinnier Wilson so much. But it is highly likely that this is due to technical problems rather than to complete absence of functional localization within the basal ganglia. The great plasticity of the nervous system can conceal the normal functions of an injured area by allowing other regions to take them over. Subtle deficits in experimental animals can only be revealed by training the animals in tasks designed to exhibit the suspected function; and this has very rarely been done. But the most difficult problem with basal ganglia disease is conceptual, on account of the nature of the symptoms themselves. Of the triad only bradykinesia can be classed as a negative symptom, potentially explicable in terms of the deletion of something by lesions of the basal ganglia; and even that is often attributed more to excessive muscular rigidity preventing movement. The other symptoms are positive. Excessive motoneuron discharge causing rigidity is 'released' by removal of inhibitory influences which might very well emanate from a site well away from the basal ganglia. Similarly basal ganglia disease may release involuntary movements and tremor 'stored' somewhere else.

Unfortunately these problems are discussed very little in this volume. Half of it is devoted to experimental studies of the basal ganglia. The experiments reported use conventional anatomical, electrophysiological and pharmacological techniques in anæsthetized animals. Behavioral or recording studies in trained animals hardly receive a mention, despite their clear promise. Anæsthetized animals cannot move. Since the diseases of the basal ganglia affect the control of movement, techniques for studying them in awake moving animals should be very fruitful. Nevertheless such studies have not been included in this report The experimental topics that are discussed, however, represent a useful summary of the present state of our knowledge.

The major inputs to the caudate nucleus and putamen (corpus striatum) come from the intralaminar nuclei of the thalamus (centromedian-parafascicular) and the cerebral cortex, particularly the association, somatosensory and motor areas. The visual cortex sends remarkably few fibres to the corpus striatum, which may well explain the relatively mild disturbance of visually-controlled movements in disorders of the basal ganglia. The projection to corpus striatum from cortical areas is roughly topographical with much overlap, whilst the projection from the intralaminar nuclei is divergent and profuse. The main outflow from corpus striatum is to both segments of globus pallidus. Also it is reciprocally connected with the substantia nigra, as is the globus pallidus itself. The radial fibres entering the globus pallidus from the corpus striatum show the interesting feature that their diameters decrease by half as they course from outer to inner segment. Presumably their conduction velocity decreases by a similar amount, but the significance of this is totally unclear. The output from globus pallidus passes to N. ventralis lateralis of the thalamus, and thence to the motor cortex. Thus a simplified information flow diagram through the basal ganglia would show cortically-processed signals passing to the corpus striatum which is reciprocally linked to the substantia nigra. From the corpus striatum signals pass to the globus pallidus, which in turn projects to motor cortex via N. ventralis lateralis thalamus. Anatomically speaking therefore, one should not view the basal ganglia as either wholly motor or wholly sensory but sensorimotor, as Teuber points out. The connections suggest that these nuclei might have something to do with transforming cortical signals into motor programmes. This idea reminds us of another subcortical structure, standing at the interface between sensory input and motor output whose precise function is also somewhat obscure—the cerebellum. Its major output is also funnelled into the motor cortex via N. ventralis lateralis thalami. Ventralis lateralis thus seems a veritable Clapham Junction of the motor system. It should be a happy hunting ground for physiologists in the future.

The electrophysiology which is reported in this volume turns out to be rather confusing however. Besides confirming the existence of anatomical pathways, conventional electrophysiological techniques hope to provide qualitative information about whether pathways are excitatory or inhibitory and quantitative information about the magnitude and timing of their effects. In the case of the basal ganglia, these simple aims have not been wholly realised as a result of the daunting complexity of the situation. Stimulation of intralaminar nuclei or cerebral cortex gives rise to short latency excitatory post-synaptic potentials (EPSPs) followed sometimes by inhibitory PSPs probably resulting from recurrent inhibition. Stimulation of caudate nucleus usually gives rise to rather long latency IPSPs in globus pallidus and substantia nigra, but sometimes also to short latency EPSPs. The neurons causing these different effects are not known. Contrary to widely held opinions the nigrostriatal axons appear to be predominately excitatory in their action, as are the pallidothalamic axons. The simple picture which can be drawn from this, of cortical and thalamic excitation feeding into the corpus striatum, which inhibits the excitation of the thalamus and hence motor cortex by the pallidum, is curiously reminiscent of the scheme which J. Purdon Martin deduced from the clinical effects of his patients' lesions. But the electrophysiological findings are so complex in detail that it is probably all too good to be true.

The most recent addition, again derived from the bedside, to the brain scientist's armoury is neurochemistry. Patients dying with Parkinson's disease were found to have pale substantia nigra, lacking the normal quantity of dopamine in the cells of the pars compacta. Miraculously, as it seemed, administration of the dopamine precursor L-Dopa which will cross the blood-brain barrier, alleviated many Parkinsonian symptoms, particularly the akinesia. Sadly the initial miracle is not sustained. New and sometimes worse involuntary movements appear after a 'period of grace', and the underlying degenerative process progresses inexorably, it seems. The new involuntary movements appear to be provoked by L-Dopa itself; and an intriguing possibility is that the symptoms are actually the result of dopamine induced overproduction of growth hormone which modifies the uptake and the gross and microscopic distribution of L-Dopa.

Though L-Dopa and the vast amount of research that its success has provoked has done a great deal for victims of some types of disorders of the basal ganglia, the work has achieved little further understanding of what the basal ganglia actually do. Dopamine is found in the nigrostriatal neurons which seem to have excitatory electrical effects on the corpus striatum and globus pallidus, though Ach-containing interneurons may be inhibited. It is secreted not only at the axon terminals in the caudate nucleus but also from dendrites in the pars reticulata of the substantia nigra. Dopamine seems likely to have a self-inhibitory effect, binding to autoreceptors on the same nigrostriatal neurons which release it, a sort of pharmacological analogue to recurrent inhibition. A further extraordinary pecularity of these cells is that they contain very large quantities of acetyl cholinesterase, which they apparently release on activity. Yet they have no certain cholinergic input at all. The functional significance of this seeming absurdity is anybody's guess. Again pharmacological studies using awake animals seem a hopeful way of trying to solve these problems.

At the moment, however, we do not have the results of such studies; and one is left rather muddled at the end of reading a volume such as this, filled with interesting yet ultimately disconnected information. In order to alleviate the muddle one still can profit by returning to the old-fashioned technique of clinicopathological correlation and the studies of J. Purdon Martin.

Martin resolved to study initially only the negative symptoms of basal ganglia disease which could more reliably be ascribed to areas of damage within them. He discovered that negative symptoms are far more widespread than is usually thought. Patients with post-encephalitic parkinsonism formed the nucleus of his studies but his observations were extended to patients with idiopathic parkinsonism, Huntingdon's chorea, hemiballismus, and Wilson's disease as well. His conclusion was that the basal ganglia are primarily concerned with the control of posture in all its aspects, from the postural relation of the parts of the body with each other to locomotion itself. He attributed the negative symptoms of the loss of control over posture to lesions of the globus pallidus. He viewed positive symptoms, such as rigidity and hemiballismus, as the release of exaggerated postural reflexes and came to the conclusion that they were dependent on intact parts of the pallidum. So, further pathological or surgical lesions of surviving pallidal neurons could paradoxically alleviate positive symptoms such as involuntary movements and tremor. He was fairly certain that there was localization of function within the pallidum, on the basis of functional groupings of postural reflexes rather than somatotopy, because he found ample evidence that labyrinthine, visual or proprioceptive reactions could be separately involved. He proposed that the subthalamic nucleus (corpus luysii) is concerned in controlling whole body reactions to unstable situations as in turning and tilting; so that when it is damaged the repository of these reactions in the pallidum is unleashed as hemiballismus. Similarly lesions in the caudate nucleus give rise to cursive hyperkinesia (running forward, even into objects, 'impelled by an irresistible drive') or milder degrees of locomotor disorder. He attributed these symptoms to failure of caudate control over a set of locomotor programmes deposited in the pallidum. Finally he ascribed rigidity and tremor to loss of control by the putamen of relevant parts of the globus pallidus. He had no ideas about what part the substantia nigra played, but we can now say reasonably confidently that it too controls the putamen and pallidum by means of its reciprocal connections with both.

In summary, Martin believed that the globus pallidus is a repository for programmes causing postural reactions, and that normally these are controlled by inputs from other parts of the basal ganglia; and as we have seen, so far as it goes, the electrophysiological evidence is consistent with this. His views are worth describing in detail because they are based on meticulous clinical observation and correlation with necropsy material; and they offer a coherent hypothesis about the functions of the basal ganglia explaining why lesions cause the symptoms they do. It is interesting that they echo the ideas of German neurologists of the 1920s such as Vogt and Kleist who thought that the basal ganglia were the repository of 'automatisms'.

There is a rather glaring deficiency in the story, however; and that is the question of their role in voluntary movement. Martin considered that any effect which disease of the basal ganglia had on voluntary movement was the result of failure of the postural reactions necessary to support it. Because the positive symptoms could be eliminated by pallidal or thalamic surgery without interfering unduly with voluntary movement, he considered that voluntary movement used entirely different pathways. It must be admitted, however, that the results of surgery are highly unpredictable, and often do in fact lead to disorders of voluntary movement. Also akinesia can be associated with little or no postural deficit or rigidity. So akinesia should be viewed as a primary symptom of basal ganglia disorders, and not merely a consequence of postural disturbances.

There is no reason why the role of the basal ganglia should be confined to automatic postural reactions, however. Denny-Brown concludes his chapter with the view that lesions of the basal ganglia delete the activating 'sets' necessary for all movements, whether postural or voluntary. And this is the view taken by Kornhuber who sees the basal ganglia as generators of function for slow pursuit movement. All these concepts have one thing in common: the idea that the basal ganglia are a site for assembling internal programmes directing movement.

It is easy to forget that, apart from the simplest reflexes, movements require far more than just a sensory trigger to start them off. They need a sequence of signals from some internal source which will move the part to its new position without the help of further peripheral stimuli. Such programmes must exist in the spinal cord and brain-stem for many reflexes. But it seems possible that for more complex postural reactions and for voluntary movements they reside within the basal ganglia. The programmes are likely to be rather stereotyped and would of course need the co-operation of other regions, most notably the cerebellum and motor cortex, to convert them into normal movements.

I am suggesting therefore that all complex movements, whether automatic or voluntary, require internally-generated sequences of signals as well as peripheral feedback for their execution. This would help explain why all types of movement can be affected by disorders of the basal ganglia. However, the class of movements known as ballistic are the easiest in which to appreciate the importance of autonomous programmes.

In executing movements the CNS uses two different modes of control. For slow 'pursuit' movements the limb is automatically locked onto its target by a system which minimizes the mismatch between limb and target. This mismatch is continuously computed from information fed back from the periphery about the progress of the movement. For such movements internally-generated programmes generated within the basal ganglia would not be so important. But for rapid movements where continuous feedback would be too slow or for movements not directed towards a particular target (for instance, expressive movements) another strategy is employed. The programme for the movement, derived from the position of the external stimulus, a memory of where it was, a prediction of where it might be or a 'mental image' of where the limb is to go, is elaborated before the movement even starts; and unfolds substantially unaltered whatever events occur during its execution. For this reason it is called ballistic control, since, like the ball leaving the mouth of a cannon, nothing can be done to alter its flight once it has started.

Movements taking less than one-third of a second and those in which there is no external target seem to be controlled in this way. Clearly the basal ganglia are most likely to be involved in such ballistic movements if the foregoing analysis is correct. So future studies in patients and in unanæsthetized trained animals should concentrate on comparing the effects of lesions and the physiological and pharmacological behaviour of the basal ganglia during ballistic and pursuit-type movements. Already a start has been made in this direction and the results appear promising. Flowers (*Brain*, **101**, 35–52) has shown that patients with Parkinson's disease are particularly bad at visual tracking when the target is temporarily blanked and the subjects have to predict where it has gone. Brooks' group in Canada has shown that local cooling of the globus pallidus in monkeys trained in a tracking task has a much more pronounced effect when the monkey is deprived of visual feedback to help him. In neither instance do control subjects find the movement any more difficult with or without visual aid. So both these observations are fully consistent with the hypothesis that the basal ganglia generate programmes for movement control independently of sensory feedback, and offer tantalizing glimpses of what the future may hold in store.

J. F. STEIN

Handbook of Sensory Physiology. Vol. 5, Part 3. **Auditory System. Clinical and Special Topics.** Edited by W. D. KEIDEL and W. D. NEFF. 1976. Pp. 811. Berlin: Springer Verlag. Price DM 288; $94.50.

The first two volumes of this series, dealing with the structure and healthy function of the auditory system, attained a recognizable anatomical, physiological and behavioural unity of purpose. But this, the third and last, falls somewhat short of that happy state as, no doubt, its own sub-title may hint. And this is a great pity, since the practising otologist struggles along in need of all the help he can get and is prepared to use.

The book begins very well. Hallpike writes a scholarly article on the nature and clinical investigation of sensorineural deafness, particularly with respect to loudness recruitment and similar derangements of the loudness function. He finally reminds us that the pure tone audiogram alone may be a poor diagnostic tool and this is of course true. In contrast many of us must have encountered psychological assessments of the nature of aphasias being done without even that minimal investigation. It is a shame that Hallpike, who writes so well, had not also dealt with the limitations of speech audiometry too. His selected references span the last fifty years of work. The most recent is from 1971 and since from other evidence it seems that the editorial office needed manuscripts by late 1975 or early 1976 there is no doubt that Hallpike had actually had time not only to read but also to assess the works he quotes. This shows in the balance and authority in his review.

There follows a chapter by Tonndorf on bone conduction. The investigation of hearing via that route is of course particularly important in diagnosing sensorineural deafness and a noble attempt is made to clarify what is an extreme complication in even the major ways by which the vibrating head eventually leads to a vibrating basilar membrane. My clinical friends will not be offended when I suggest that the mathematical equipment needed fully to understand these linkages is not given to us all: so here perhaps is the first of the undefined 'special topics'. This one is quite close to clinical practice and Tonndorf's summary, page 79 onwards, of the final consequences of all the mechanics, is well within the reach of a general understanding and essentially points out what is really happening in the Weber and Rinné tests. Let us be grateful for their practical efficacy in the face of such theoretical complexity.

If Tonndorf's article has some clinical relevance, this is very hard to find in Geislers' on mathematical models of the mechanics of the inner ear. Most otologists and not a few engineers will find this one very hard going and the clinicians, who least of all need to be told that the cochlea is complicated, will find little resolution of their difficulties there. Steele's article on cochlear mechanics must also be 'special' with its multiple integrals eventually showing that 'the cochlea is by no means representable by a simple wave equation'; only the purest of pure physiologists would dare to consider its behaviour linear. But apart from a useful phrase or two like that, in the prose between the equations, these two articles would have been very much less out of place in the earlier volumes.

Hallowell Davis introduces electrical response audiometry (ERA) with special reference to vertex potentials. His article may be well liked by clinicians beginning to be interested in the possible uses of ERA. He has a variety of useful tips and surveys the field from 1935 to 1972 calmly and not over optimistically. The problem of whether a neonate with a normal ERA can necessarily hear normally, in its fullest sense, is of course not easily resolved and Davies sensibly does not try to do so.

But then the floodgates open. Keidel, a pioneer in the field, it is true, gives us 125 pages on the physiological background to ERA plus a total of 606 references, 523 of them from the 1960s and 1970s, one from the year of publication of this volume (in preparation) and even one (Montandon *et al.*, p. 223) alleged to be from 1985! There follow another 75 pages on ERA, on clinical experience by Zöllner and Strange, and on habituation and attention in ERA work by Picton, *et al.* There is also a later chapter by Eggermont on the more peripheral but conceptually related, though invasive, techniques of electrocochleography. This in a further 79 pages.

Inevitably an explosion in the literature on such techniques has followed with not too great a lag the development of automatic computational techniques that allow small signals to be pulled out from the noise. But, and perhaps therefore, there is very much the impression in these accounts of critical indigestion following a too rapid intake of numbers and graphs. They will no doubt help the jobbing research otologist by encompassing, if in nearly 40 per cent of this volume, the much more vast output of original papers on these topics. But until it is actually decided what in fact it is worth while to measure in ERA the clinician will be little helped in assessing its routine clinical value by catalogues of all attempts. When the happy day arrives that matters are better understood, the all-purpose computer which frightens the otologist—and he is not alone—will be set aside and a less flexible but more specialized black box containing appropriate microprocessors will be available to him. In will go the signals and out may come one or two numbers as useful in auditory diagnosis as are the two or three readings from a sphygmomanometer to the cardiovascular specialist. But not yet.

An article of immediate clinical utility is Hawkins' on drug ototoxicity and vestibular toxicity. This deals particularly with the aminoglycosides and the problems in balancing their antimicrobial virtues against their cochlear damage. He also describes the auditory perils of ethacrynic acid and furosemide and underlines the particular dangers of using these diuretics together with the aminoglycosides. These matters are also referred to in an earlier chapter by Wigand who points out relationships between vestibular disorders and accompanying nephritis that are not just attributable to drugs used in the renal treatments.

Clinico-legal considerations presumably inspired much of the work that leads to Connor and Rudmose's detailed article on community responses to noise and probably also to Gierke and Parker's studies on infrasound. Nevertheless to those of us who are not too close to those fields there is some fascinating data here that often illuminates the pure science.

Only marginally related to the clinic is de Boer's 106-page monograph (Chapter 13) on the residue and auditory pitch perception. Those most interested in using these peculiar sounds to disentangle the problems of hearing the real sounds of nature are unlikely in these days of high book prices to buy this clinically biassed volume for that article alone. Likewise the clinician may feel cheated that 14 per cent of his DM 288 is devoted to the highest flights of the nonlinear psychophysics of pitch perception. Volume 2 was probably the place for it.

What de Boer's article does do is to underline the most glaring gap in our knowledge of the auditory system, i.e. in deciding what it is that comes out in the eighth nerve that is actually used in hearing. Essentially we do not know; though there are some clinicians who are prepared to stimulate the auditory nerve in man with implanted electrodes in the hope of finding a useful prosthesis for those deafened by cochlear damage. Simmons describes some of this work, and his chapter is followed by an assessment by Gerken of the utility of observing the behavioural responses of animals to electrical stimulation of the auditory system.

Most auditory physiologists accept today the existence of a tightly tonotopic functional organization throughout the auditory pathways. This is not altogether surprising, considering the retinotopicity of the visual system and the analogous somatotopicity for tactile sensation. Spatial organization on the retina has to do with objects in the outside world. The fields of the cutaneous receptors and the somatotopic pathways are concerned with spatial analysis of external objects touching the skin. But on the internal carpet of mechanoreceptors of the basilar membrane it is frequency that has a lot to do with the spatial pattern of the receptors' excitation and auditory tonotopicity and frequency analysis is the 'place theory' analogue of the other two systems' preservation of pattern in their own functional analysis of external place. This tonotopicity is strictly preserved and elaborated from the cochlea onwards to the middle layers of the primary auditory cortex. It is unlikely that it can be mocked, as it is by gross stimulation of the auditory nerve with a few electrodes. One predicts that only a relatively trivial auditory benefit can be expected in the near future from such devices until tonotopicity can also be fully exploited.

There is in fact no mention in the whole of this volume of Merzenich and associates' meticulous studies of the tonotopic cortex between 1973 and 1975. Clinicians are therefore recommended to study a recent summary of the matter. (Merzenich *et al.*, 1977. Some basic features of the organization of the central auditory nervous system. In: *Psychophysics and Physiology of Hearing*. Edited by Evans and Wilson. Academic Press.) The devil's advocate will reply that this is too recent to assess properly; nevertheless what has so far been found should be a powerful inhibition to undue optimism about present cochlear implants in man.

In conclusion, this volume, though mixed in its appeal, containing some strange bedfellows and lacking some matters of important clinical interest (for example, the epidemiology and embryology of disorders of audition) is nevertheless stimulating. There should be a place for it on the shelves of any serious otological department, clinical or research.

R. H. KAY

Hypothalamic Peptide Hormones and Pituitary Regulation. Edited by J. C. PORTER. Vol. 87 of Advances in Experimental Medicine and Biology. 1977. Pp. 366. New York and London: Plenum Press. Price $39.00.

The book contains the Proceedings of the Third Workshop Conference on Neuroendocrinology held during November 1976 in Bethesda. New aspects of the function of peptide hormones are prominent in the various lectures. Thus the multiple sites of occurrence and formation of releasing factors, initially presumed to be entirely of hypothalamic origin, have led to assigning various central and peripheral actions to these substances; furthermore, there are the surprising changes in activity produced by peptides which break up into fragments exhibiting agonist, antagonist, or completely new properties. Much emphasis is laid on interaction of peptides and brain amines. New therapeutic hopes are raised by the possibility of synthesizing releasing factor analogues which can act as antagonists.

There is yet another direction in which our thinking will have to be re-orientated: whereas it has been known for many years that the direction of the blood flow in the hypophyseal portal vessels is directed from hypothalamus to the distal lobe of the pituitary, another group of vessels situated in the subependymal plexus of the stalk, bringing blood from the neural lobe towards the brain, has been shown of equal functional importance. Porter and co-workers had the idea of introducing a cannula *pointing towards the median eminence* into a portal vessel. They compared the concentrations of LH, TSH, ACTH, prolactin and vasopressin in the portal venous blood with that in arterial blood and found the concentrations in the former invariably very high. This 'retrograde' transport of pituitary hormones permits agents from the neural lobe to influence the distal lobe, and all pituitary secretory products to reach the brain without first being diluted or trapped in the peripheral circulation.

This thought-provoking volume will be of interest to a wide and varied readership.

MARTHE VOGT

Biochemical Correlates of Brain Structure and Function. Edited by A. N. DAVISON. London: Academic Press. 1977. Pp. 345. Price £14.00; $27.35.

This book contains nine reviews, by different authors, of recent developments in neurochemical research. All are concerned primarily with the interrelation of structure and function, but implications for future work abound, and there are many indications of possible clinical applications of this new information. The book begins with three chapters in which the role of metabolic factors in brain development is reviewed. The critical role of ribonucleic acid metabolism receives particular emphasis. For neurologists and psychiatrists Crow's account of the structure and function of monoaminergic pathways in the central nervous system is especially useful in view of the increasing relevance of such information in clinical practice. Dopamine, noradrenaline, adrenaline, and serotonin are discussed in relation to their role as central neurotransmitters. In recent years it has been shown that cerebral blood flow is determined by underlying local changes in intermediary metabolism. These are discussed by Siesjö in a well-organized review of the physiologically important factors regulating the supply of oxygen and glucose, and the relation of metabolic rate to the metabolic state of the brain. Finally, three chapters deal with various aspects of behavioural neurochemistry. Brain peptides, first described in relation to pituitary function, are discussed in the wider context of their role in memory processes in the rat, and the wider problem of the biochemistry of learning and memory receives critical consideration; 'what biochemistry can at best provide is a description of learning, its explanation in molecular terms, but not its prediction or control'. The ancient and mysterious problem of sleep forms a fitting last chapter. Here again, brain peptides are important. Like all biochemical treatises the book abounds in cryptic symbols and abbreviations, but these are all properly explained for the uninitiated and the book, throughout, is concerned with principle rather than detail. Although the book is primarily concerned with brain biochemistry in species other than man, it should be widely read.

MICHAEL SWASH

Handbook of Clinical Neurology. Edited by P. J. VINKEN and G. W. BRUYN. Vol. 24. **Metabolic and Deficiency Diseases of the Nervous System.** 1977. Pp. 570. Amsterdam: North Holland. Price Dfl. 209.00.

This volume completes the group of three dealing with metabolic and deficiency diseases of the nervous system. The first chapter covers the effects of nutritional deprivation on the developing nervous system, a topic familiar to British neurologists particularly through the work of Dobbing. In the second chapter Moser considers aspects of amino acid metabolism which are of particular significance to nervous function. The major content of the book is found in subsequent chapters dealing with a wide range of hereditary metabolic disorders affecting the nervous system. Familiar subjects include phenylketonuria, maple sugar and Hartnup diseases, the lipidoses, Lesch-Nyhan syndrome and disorders of fructose and galactose metabolism. Less familiar disease states are amply dealt with, and there is a comprehensive review of Reye's syndrome. The work concludes with chapters by Aquilonius and Fahn on central nervous transmitters and Hornkiewicz on biogenic amines in the nervous system. Paediatric neurologists will find the volume a valuable work of reference; it does not lend itself to sequential reading in the way some earlier volumes have done so successfully. Clinicians working with older patients will find less to appeal to them.

R. A. HENSON

Handbook of Clinical Neurology. Edited by P. J. VINKEN and G. W. BRUYN. Vol. 31. **Congenital Malformations of the Brain and Skull,** part II. Pp. 642. Amsterdam: North Holland. Price Dfl. 245.00.

Volume 31 of the Handbook is the second of a series on congenital malformations of the brain and skull. The editors explain that the book has been published in advance of Volume 30; they also defend the inclusion of topics covered in earlier volumes. Thus, there is an excellent, but relatively brief, chapter on the phakomatoses and a lengthy piece by Lagos on vascular anomalies in infancy, childhood and adolescence. While this latter chapter is helpful it is inevitably repetitious in several parts. On the other hand, the sections dealing with congenital tumours and 'congenital arachnoid' cysts are extremely valuable. Cox and Ray give an account of the human chromosomes and their aberrations, while Zellweger and colleagues provide authoritative descriptions of Down's syndrome and other chromosomal aneuploides. Other chapters deal with the effects of various intra-uterine infections, growth deficiency syndromes and skeletal anomalies with neurological malformations, and these are comprehensively informative.

R. A. HENSON

Aging and Dementia. Edited by W. LYNN SMITH and MARCEL KINSBOURNE. 1977. Pp. 256. New York: Spectrum. Price £11.25.

Currently dementia is regarded as an inevitable and permanent disorder making its diagnosis almost synonymous with 'no treatment'.

It is estimated that about 10 per cent of the population over 65 years old are affected and with extended longevity the problem is exacerbated. The factors distinguishing senescence from senility thus become of more than academic interest. The question as to whether or not senile dementia is simply exaggerated aging or if it is a distinct pathological process is a major theme in the book.

In his review of morphological changes in dementia and old age, Tomlinson concludes that loss of neurons rarely accounts for dementia and other changes interfere with cerebral function. Chapters on vascular disease and on radiographic morphology of cerebral atrophy are highly relevant to this hypothesis. The recent work suggesting that in dementia there is a selective loss of neurons or synapses is not discussed. Only about one fifth of cases can be attributed to arteriosclerosis. In addition, as indicated by Gajdusek and his colleagues, in a long authoritative chapter, the rare Creutzfeldt–Jakob disease is a transmissible slow virus form of dementia. Of 35 patients with Alzheimer's disease, 2 with a familial history proved to be atypical cases of transmissible virus dementia but here the Creutzfeldt–Jakob agent may be acting as a secondary pathogen. Otherwise the ætiology of Alzheimer's disease remains obscure Besides dealing with some of these topics, other contributors review some of the intriguing information about the behavioural correlates of aging and mental disorder.

This is an interesting, readable and thoughtful book which can be recommended to those concerned with the general problems raised by the aging of the human brain.

A. N. DAVISON

Neurological Classics in Modern Translation. Edited by D. A. ROTTENBERG and F. H. HOCHBERG. Pp. 324. New York: Macmillan. Price $22.50.

The neurological classics contained in this book derive from continental Europe, not Europe in the contemporary sense of the term. The editors have sought to provide 'English-speaking' medical students, physicians and surgeons 'with ready access to some of the most significant—and, in several instances, most controversial—contributions of nineteenth and twentieth century European neurology'. Sections on morphology, presenile dementia, alcoholic dementia, myoclonic dementia, dysphasia, dyspraxia and disorders of the body image, pain and sensibility, spinocerebellar degeneration, narcolepsy and infectious polyneuritis are introduced by American neurological scientists.

The papers selected for inclusion have been well chosen, but as Raymond Adams remarks, 'one may discover that the original description was so imprecise that even when accurately reproduced or translated it is impossible to decide what was being described'. Thus, E. P. Richardson, in his introduction to Creuzfeldt's and Jakob's papers, suggests that the reader can decide whether either of them described CJD. However, it is a rewarding experience to read or re-read these seminal works, for example Cajal's (1892) 'New concept of the histology of the central nervous system', Pick and Alzheimer on presenile dementia, Wernicke on his disease, and Guillain, Barré and Strohl's short initial description of Guillain–Barré Syndrome. Liepmann's (1900) account of his examination of an apraxic patient still impresses as an example of the careful way in which German neurologists explored the neuropsychological aspects of a case. There are even flashes of humour to reward the diligent reader; Wernicke's Case 2 was an '. . . alcoholic Scots piano teacher, who called himself a professor', while the story of Gélineau's Case 1 of narcolepsy contains a moral more popularly associated with British literature of the time (1880).

This book is recommended to all neurologists unfamiliar with the early continental European neurological literature in the original. British neurologists, though perhaps only the more ancient ones, still turn to Gowers' (1886) with enlightenment, and they can also benefit from Doctors Rottenberg and Hochberg's enterprise. Translations have not been checked against the originals by this reviewer, but they read well. The publication is handsome and the price reasonable.

R. A. HENSON

Radiologic Anatomy of the Brain. By G. SALAMON and Y. P. HUANG. 1977. Pp. 404. Berlin: Springer. Price DM 360.00.

The Departments of Radiology at Hôpital de la Timone, Marseille, Mount Sinai Hospital and School of Medicine of the City University of New York have combined to produce a lavish and beautiful book of anatomy especially suited to clinicians and to neurophysiologists. Academic anatomists may also find it very interesting because, among many other facets, they will find chapters relating the intracranial arteries and veins to the macroscopic features of the brain in a more detailed way than is given in standard texts. This sort of anatomy is well based on radiology and has been elaborated by three generations of neuroradiologists.

Throughout the book it is the inter-relationships of structures that have been emphasized, attention is constantly drawn to how the cortical sulci relate to the skull, the arteries to the sulci, the vessels to the ventricles and cisterns and the section to its superficial orientation. It is full of helpful diagrams and extensively labelled photographs and radiographs. It is an essential reference book for every neurology, neurosurgery, neuroradiology and neurophysiology department.

G. DU BOULAY

Language. Its origin and its Relation to Thought by F. R. H. ENGLEFIELD. Edited by G. A. WELLS and D. R. OPPENHEIMER. 1977. London: Elek/Pemberton. Pp. 192. Price £6.00.

In the days when one spoke of philology, a number of brilliant, well and clearly written volumes were published and acclaimed for their wisdom, profundity and their wit. Where are the modern counterparts? With its aggrandisement into linguistics, the subject began to alter sadly and has led to considerable confusion in thinking, and still more in expression. Gobbledeygook became the occupational affection of those who set out as specialists in the phenomena of language. In their pride many sought to ally linguistics with logic, psychology, phonetics, philosophy, neurology, and even mathematics.

It is long since one has read such a sensible little monograph, written with due respect to the Queen's English, as Ronald Englefield's present study. The author, unfortunately no longer living, is admirably introduced to us in a charming fashion by two eminent admirers, namely Professor G. A. Wells and Dr. D. R. Oppenheimer.

Englefield, they point out, was a shrewd and erudite iconoclast. Lenneberg comes under a mixed reception. He is praised by Wells and Oppenheimer for his valuable book, which would have been even better if he had made the extra effort to write in simple and intelligible prose, and if he had not strayed into the desert of Chomskyan metaphysics.

Englefield believed that all natural forms of communication depend on perceptible utterance or visible signs. Speech, gesture and writing correspond approximately to audible, visible and durable types of signs. The relationship of signs and language is intimate and Englefield discussed the *modus operandi* in considerable detail. He did not consider this relationship had been in any way helped by the theories of Piaget which he regarded as implausible. Gesture-language was well but not exhaustively described, and written as well as spoken speech are traced in their development from form to symbol.

Englefield originally wrote a twelve-chapter volume, but the bold prefatorial-writers fortunately added for our delight or for our exasperation, a thirteenth chapter gleaned from scattered critical comments upon the ideas of a number of contemporary oracular sources. Diamond's views upon the history and origin of language are the first to suffer. He does not agree in the primacy of the verb nor with all its alleged properties. Among animals, the connection between their gestures and their calls does not correspond with the author's experience. Englefield would have no truck with Révész's 'pre-forms' and 'protoforms' of language, regarding this talk as little more than juggling with definitions, bearing no relation to experience or to established facts. Most gratifying is Englefield's non-acceptance of the modern apotheosis of Chomsky and his obsession with grammar. As Englefield said 'the important thing about a word is its meaning, that is to say, what it denotes. Chomsky's writings are grammatically correct; his sentences contain subject, verb and predicate, but to me they are often unintelligible because of their vocabulary'. The 'deep structure' so dear to Chomsky is but a phrase which stands for no intelligible mental operation. Even as an antidote to Watson's behaviourism, Chomsky's ideas are not unique.

Finally, we are regaled with some well-reasoned and well-expressed criticisms of Bertrand Russell and A. J. Ayer. Let us quote Englefield: 'The attempt to arrive at truth through the manipulation of words is a centuries-old philosopher's dream. It is partly based on the notion that language is, or could be made to be, a symbolic *system*, analogous to mathematics, which enables the user to infer the nature of reality from a proper manipulation of the symbols. I have endeavoured to show that this is an illusion. No inferences drawn from an arbitrary system of symbols can have any significance except in relation to some other correlated system. The only correlated system that could be claimed for language would be the whole system of nature; and for such a purpose the trivial resources of language, even if all the contrivances of grammar and syntax of all the languages in the world were combined and all their vocabularies added together, would be utterly inadequate. If, therefore, the philosopher—as Ayer assures us—is really restricted to propositions about language, to definitions and inferences from definitions, and is debarred from making any use of experimental facts, then it is not possible that he should make any contribution to knowledge.'

Finally, one may turn back and read with appreciation the author's own brief preface in which he introduces Dinah and Sarah, his two Labrador bitches, who afforded him a wealth of mental inspiration as well as companionship.

MACDONALD CRITCHLEY

FORTHCOMING EVENT

THE Second International Child Neurology Congress will be held in Sydney between November 26 and 30, 1979. Further particulars may be obtained from:

Second International Child Neurology Congress
GPO Box 3866
Sydney N.S.W.
Australia 2001.

Brain

General Index

A re-issue of the first part of the General Index, covering Volumes 1–23 (1878–1900) and a recently compiled second part covering Volumes 24–48 (1901–1925) are now available to subscribers at £2·00 each, postage Part 1 (25p) Part 2 (20p) Parts 1 and 2 (40p). A third part (1926–1950) will follow.

Please write, enclosing money with order, to:
Wm. Dawson and Sons Ltd.,
Back Issues Department,
Cannon House,
Folkestone, Kent CT19 5EE, England.

Back issues of BRAIN can also be obtained from Wm. Dawson and Sons Limited. Please apply direct for prices and availability.

CHARLES C THOMAS • PUBLISHER

HOW TO EXAMINE THE NERVOUS SYSTEM: Techniques and Methods *by* **R. T. Ross,** *Univ. of Manitoba, Winnipeg, Manitoba, Canada.* Presented in a uniquely appropriate format, this monograph will provide the medical student with the skills needed for examination of the nervous system. Chapters include information on the fundus oculi, the ophthalmoscope, central and peripheral vision; eye movement; cranial nerve involvement; arms and legs, posture, rapid alternating movements, muscle tone, power and bulk; stance, gait and balance; reflexes; sensation; the corticospinal tract syndrome; cerebellar signs; and intellectual assessment. *'78, 136 pp. (4 1/2 x 7), 44 il., $6.50, Lexide*

THE CERVICAL SYNDROME (4th Ed.) *by* **Ruth Jackson,** *Southwestern Medical School of The Univ. of Texas, Dallas, Texas. Foreword by* **A. Steindler.** For this new edition, the author continues to stress the basics: fundamental anatomy, a careful patient history, meticulous examination, and adequate radiography. Improvements, additions and innovations, however, characterize every aspect of this new version of an established text. The anatomy of the cervical spine, the etiology of responsible factors, symptomatology, and clinical findings all receive expanded coverage. The sections on radiography and treatment have also been updated. *'78, 416 pp., 459 il. (7 in color), $19.50*

FUNDAMENTALS OF VISCERAL INNERVATION *by* **Budh Dev Bhagat** *and* **Paul A. Young,** *both of St. Louis Univ., St. Louis, Missouri, and* **Donald E. Biggerstaff,** *Southern Illinois Univ., Springfield, Illinois.* Extensive coverage is given to the most recent advances concerning the mechanisms of synthesis, release and inactivation of neurotransmitters at neuroeffector junctions in the viscera. Anatomy, physiology and pharmacology have been integrated to present the subject in a unified and logically organized manner. The use of abundant anatomical illustrations will help the reader to grasp the subject thoroughly and easily. *'77, 216 pp., 91 il., 18 tables, cloth-$24.75, paper-$16.75*

EPILEPSY AND YOU *by* **Frank O. Volle,** *Consulting Practice, and* **Patricia A. Heron,** *Denver Mental Health Center, both of Denver, Colorado.* Written by two clinical psychologists for epileptics, their families and friends, this book discusses the problems that epileptics must face. A definition of epilepsy is included along with information on finding the right doctor, the uses and abuses of medicine, getting a job, driving a car, and prospects for the future. The differences between youth-onset and adult-onset epilepsy are outlined. The text is geared to both adolescent and adult readers. *'78, 84 pp., 1 table, cloth-$8.50, paper-$4.95*

REFLEX TESTING METHODS FOR EVALUATING C.N.S. DEVELOPMENT (2nd Ed., 6th Ptg.) *by* **Mary R. Fiorentino,** *Newington Children's Hospital, Newington, Connecticut. Foreword by* **Burr H. Curtis.** This practical book on the examination of infants and young children can be used in the diagnosis and evaluation of abnormal reflexive actions. Assessment of other patients who may need neurophysiologically oriented treatment is included. A section is provided on determining maturation level and abnormal reflexes for a treatment program. *'77, 72 pp. (6 3/4 x 9 3/4), 78 il., 1 table, $8.50*

ATLAS OF BRAIN ANATOMY FOR C.T. SCANS: Using EMI Terminology (2nd Ed.) *prepared by* **Fred C. Shipps, J. McAndrew Jones** *and* **Anthony D'Agostino,** *all of Good Samaritan Hospital, Portland, Oregon.* This book continues to offer a rapid and convenient review of cross-sectional anatomy of the brain as found on C.T. scans, but many additions and revisions have been made for this edition to maintain currentness. New chapters are included on the identification of common artifacts; window width, window level, and mu; transferring C.T. findings to the lateral skull film; and a method of clinicopathological correlations. A section on skull anatomy using the EMItronic Model 5000 Scanner is also presented. The unique self-teaching feature of the original edition — the overlay format — has been retained. *'77, 60 pp. (8 1/2 x 11), 82 il., $16.75, spiral (paper)*

Orders with remittance sent by air, postpaid

301-327 East Lawrence Avenue • Springfield • Illinois • 62717 • USA

PRINTED IN GREAT BRITAIN AT THE UNIVERSITY PRESS, OXFORD
BY VIVIAN RIDLER, PRINTER TO THE UNIVERSITY

Rec. 13.2.79

ISSN 0006-8950

Brain

A Journal of Neurology

Volume 101 Part III September 1978

Bilateral Tactile Aphasia: A Tacto-verbal Dysfunction. Marie-France Beauvois, Brigitte Saillant, Vincent Meininger and François Lhermitte 381

The Neuroanatomy of Amnesia: A Critique of the Hippocampal Memory Hypothesis. James A. Horel 403

Electroencephalographic Studies of Myoclonus: Myoclonus-related Cortical Spikes and High Amplitude Somatosensory Evoked Potentials. Hiroshi Shibasaki, Yoriaki Yamashita and Yoshigoro Kuroiwa 447

Familial Myoclonic Epilepsy with Ataxia and Neuropathy with Additional Features of Friedreich's Ataxia and Peroneal Muscular Atrophy. N. J. Smith, M. L. E. Espir and W. B. Matthews 461

Sensory Action Potentials and Biopsy of the Sural Nerve in Neuropathy. F. Behse and F. Buchthal 473

Factors Influencing the Risk of Multiple Sclerosis Developing in Patients with Optic Neuritis. D. A. S. Compston, J. R. Batchelor, C. J. Earl and W. I. McDonald 495

The Intrinsic Connections of the Cortex of Area 4 of the Monkey. K. C. Gatter and T. P. S. Powell 513

An Electron Microscopic Study of the Termination of Intracortical Axons upon Betz Cells in Area 4 of the Monkey. K. C. Gatter, J. J. Sloper and T. P. S. Powell 543

Notices of Recent Publications 555

OXFORD: AT THE CLARENDON PRESS

Edited by C. G. PHILLIPS
Deputy Editor R. A. HENSON
with the help of

J. HUME ADAMS R. W. GILLIATT M. VOGT
A. N. DAVISON E. C. HUTCHINSON L. WEISKRANTZ

Assistant Editor E. MACDOUGALL
Secretary and Treasurer J. M. NEWSOM DAVIS

All editorial correspondence, typescripts and books for review to be addressed to The Editor of *Brain*, Hertford College, Oxford, OX1 3BW

Directions to Authors upon the Preparation of Papers

PAPERS must be typewritten on one side of the paper only and double-spaced, and submitted in duplicate with two sets of figures. In addition to the full title of the paper, authors should supply a 'running title' which will appear at the heads of the pages. *Brain* does not publish preliminary reports of work in progress: only exceptionally does it publish detailed studies of a single case. The typescript should be carefully and finally revised before submission to the Editor, so that if the paper is accepted it is ready for the printer Clarity of style and brevity of expression are essential. Before submitting a paper it is always valuable to obtain the comments of colleagues who are unfamiliar with the work. We refer intending authors to the *Journal of Physiology*'s 'Suggestions to Authors' price 10p post-free from Cambridge University Press, Box 92, 200 Euston Road, London, NW1.

The paper should be accompanied by a declaration in the following terms: 'The work reported in the attached paper entitled . has not been, and is not intended to be, published anywhere except in *Brain* '

BIBLIOGRAPHIC REFERENCES should be limited to essential literature, they should be listed at the end of the paper in alphabetical order, and not numbered *In the case of a Journal*: author's name, date of publication in brackets. are followed by the title of the paper, the name of the Journal *in full* and underlined for italics, the volume number and the first and last page numbers of the paper quoted, both in Arabic numerals. *In the case of a book*: author's name, date of publication in brackets, title of book underlined for italics, place of publication, publisher's name, chapter and page numbers in Arabic numerals Works by the same author should be given in chronological order, and if there be more than one in a year, they are marked *a*, *b*, *c*, etc.; when an author's name recurs a short line is used. *In the text* numbered references are not used, but the author's name is followed by the appropriate year in brackets.

ILLUSTRATIONS should, where possible, be line drawings in Indian ink on separate white boards, numbered, and with the author's name on the back Drawings and other illustrations should not exceed twice the size of the reproduction and thus lines must be thick enough to show up after reduction. This applies also to the lettering and numbering which the authors are asked to provide Legends should be on separate sheets and numbered. Desired positions of tables and figures should be marked by writing instructions enclosed within lines and brackets, e.g. *(Table 3 near here)* or *(Fig 4 near here)*.

Half-tone photographs must be kept to a minimum. Excellent photographs with clear contrast are essential, especially for the reproduction of electron micrographs Authors may be asked to contribute to their cost. There should be a bar on all micrographs giving magnification, e.g. 1 μm.

Authors are asked not to reprint their papers, or to authorize others to do so, without first consulting the Oxford University Press (Academic Division), Walton Street, Oxford, OX2 6DP.

Fifty free offprints are sent to the authors, who may order more direct from Oxford University Press, Walton Street, Oxford, OX2 6DP when they get their proofs.

Subscription rate for an annual volume of four issues. £19.00 ($42) post free, or for subscribers resident in the U K. £16 50 Single Issue: £5.00 ($12) net, postage extra.

Please address correspondence on business matters as follows:

Subscriptions to the current volume: Subscriptions Department, Oxford University Press, Press Road, Neasden, London, NW10 0DD.

Orders and inquiries for back numbers Wm. Dawson & Sons Limited, Cannon House, Folkestone, Kent.

Inquiries about advertising, offprints and copyright: Academic Division, Oxford University Press, Walton Street, Oxford, OX2 6DP.

Brain

A Journal of Neurology

Volume 101 Part III September 1978

Bilateral Tactile Aphasia: A Tacto-verbal Dysfunction. Marie-France Beauvois, Brigitte Saillant, Vincent Meininger and François Lhermitte 381

The Neuroanatomy of Amnesia: A Critique of the Hippocampal Memory Hypothesis. James A. Horel 403

Electroencephalographic Studies of Myoclonus: Myoclonus-related Cortical Spikes and High Amplitude Somatosensory Evoked Potentials. Hiroshi Shibasaki, Yoriaki Yamashita and Yoshigoro Kuroiwa 447

Familial Myoclonic Epilepsy with Ataxia and Neuropathy with Additional Features of Friedreich's Ataxia and Peroneal Muscular Atrophy. N. J. Smith, M. L. E. Espir and W. B. Matthews 461

Sensory Action Potentials and Biopsy of the Sural Nerve in Neuropathy. F. Behse and F. Buchthal 473

Factors Influencing the Risk of Multiple Sclerosis Developing in Patients with Optic Neuritis. D. A. S. Compston, J. R. Batchelor, C. J. Earl and W. I. McDonald 495

The Intrinsic Connections of the Cortex of Area 4 of the Monkey. K. C. Gatter and T. P. S. Powell 513

An Electron Microscopic Study of the Termination of Intracortical Axons upon Betz Cells in Area 4 of the Monkey. K. C. Gatter, J. J. Sloper and T. P. S. Powell 543

Notices of Recent Publications 555

A COMPLETE REVIEW OF THE MEDICAL

Core Journals in Clinical Neurology offers you these features:

Abstracts Core Journals in Clinical Neurology provides you with abstracts of all original articles published in the world's best clinical neurology journals:
Annals of Neurology - USA. Brain - United Kingdom. Journal of Neurology - GFR. Journal of Neurology/Neurosurgery and Psychiatry - United Kingdom. Neurology - USA. Revue Neurologique - France. Journal of Neurological Sciences - Netherlands.

Table of Contents Each issue of Core Journals in Clinical Neurology provides complete tables of contents from these carefully selected journals:
The New England Journal of Medicine - USA. The Journal of the American Medical Association - USA. The Lancet - United Kingdom. British Medical Journal - United Kingdom. Deutsche Medizinische Wochenschrift - GFR. La Nouvelle Presse Médicale - France.

Core Journals in Clinical Neurology - a matter of efficiency.

Experience has shown that in any medical discipline, as many as 80 percent of the most significant developments are published in approximately 20 percent of the journals in that specialty area. With this in mind our editorial staff of clinical neurological specialists collate, translate when necessary, prepare and publish abstracts of all original articles of the most important journals. Each month Core Journals in Clinical Neurology gives you more information in less time.

Core Journals in Clinical Neurology - designed for you, the practitioner.

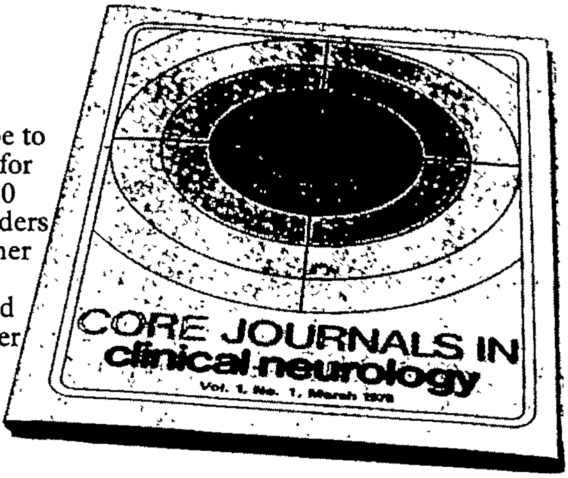
By virtue of their own experience in clinical neurology practice, the editors of Core Journals in Clinical Neurology have carefully selected the journals which offer the most valuable material to your own practice. Emphasis is placed on selecting and abstracting only those journals offering practical application of new diagnostic and therapeutic findings to the practice of clinical neurology.

Core Journals in Clinical Neurology one of the fastest current awareness services.

Monthly publication permits the publication of an abstracted article and its appearence in Core Journals in Clinical Neurology within six weeks or less after its original publication. This makes Core Journals in Clinical Neurology one of the fastest current awareness services in the world.

30-MINUTE WORLD'S TOP JOURNALS.

Subscription costs, only 85 Dutch Guilders.
As a practitioner, you can subscribe to Core Journals in Clinical Neurology for 1978 for only 85 Dutch Guilders or 40 percent less than the 135 Dutch Guilders subscription rate for libraries and other institutions. The first issue is dated March so ten issues will be published this year. If your order is received later in the year, you will be invoiced on a pro rata basis.



BR

Put it to the test.

☐ send me a free sample (and I have no obligations)

☐ yes, I am interested - enter my individual subscription to Core Journals in Clinical Neurology

☐ yes, I am interested - enter my institutional subscription to Core Journals in Clinical Neurology

☐ I await your invoice ☐ I enclose my check

Please complete the following in capital letters

Name: ____________________

Address: ____________________

Date: ____________________

Signature: ____________________

Please return the order form to: Core Journal Publications, P.O. Box 1126, Amsterdam, The Netherlands.

Watch out for
Trends in NeuroSciences

the key to better communication between clinicians and researchers involved in neuroscience.

Advisory editorial board
C BLAKEMORE, Cambridge, U K F E. BLOOM, San Diego, CA., U S.A W M COWAN, St Louis, MO , U S.A O D. CREUTZFELDT, Gottingen, Germany T J CROW, Harrow, U K T HOKFELT, Stockholm, Sweden M ITO, Tokyo, Japan L L. IVERSEN, Cambridge, U K H L KLAWANS, Chicago, ILL , U S A. R PORTER, Clayton, Vic., Australia D P. PURPURA, New York, N Y , U S.A J E. TREHERNE, Cambridge, U K J N WALTON, Newcastle-upon-Tyne, U K D DE WIED, Utrecht, The Netherlands.

Staff editor
M B TER HAAR, Cambridge, U K

The first issue of Trends in NeuroSciences comes out in July If you are concerned with any of the fields involving the brain including neurochemistry, neuropharmacology, neuroendocrinology, psychology, neurology, ethology, psychiatry, anaesthesiology, neurophysiology, neuropathology, neurogenetics or psychopharmacology, TINS will be of interest to you. The articles and reviews in Trends in NeuroSciences will not simply reflect current research in any one area but will also stimulate discussion and comment between specialists in the hope of creating an intelligible dialogue across the entire spectrum of neuroscience and neurology

The following are titles of some of the articles which will be appearing in the first three issues

Leader Article
Communication in the Neurosciences, *F E Bloom and T. Melnechuk*

Neuroscience News
Japan - Brain Research Joint Meeting in Japan, *K Obata* Mechanisms of Action of Benzodiazepines, *M B. ter Haar*

Neuroscience Centres of the World
The Neurosciences at Monash University, Australia, *L M Aitkin.*

Perspectives
In Memoriam· *Dr. James L O'Leary by W M. Cowan.*

Points of View
Concept of Schizophrenia - the differing views of *R E Kendell and T Szasz*

Review Articles
The Aetiology and Pathogenesis of Early Infantile Autism, *L Wing.* Huntington's Disease (Chorea), *E D Bird* Lessons for the Lesch-Nyhan Syndrome, *R W E Watts* Neurophysiology of Feeding, *E T Rolls* Olfaction and Taste - Dual Systems for Sensory Processing, *E.B. Keverne* Nervous Control of the Ovary, *H W. Burden* Enkephalins and Endorphins, *R J Miller.* Mechanisms of Echolocation in Bats - Comments on the Neuroethology of the Biosonar System of 'CF-FM' bats, *N. Suga and W E O'Neill.* Anxiety, ACTH, and 5-HT, *S E File* Steroid Hormone Receptors in the Brain, *B.D. Greenstein*

Techniques and their uses
Acupuncture Analgesia, *P W Nathan.*

Neurotransmitters
Chemical Messengers in the Brain, *L L Iversen* (Introduction to series).

Neuroplasticity
The Case for 'Relevance' in Sensorimotor Physiology, *R Granit.*

Personal edition
Special introduction offer of 6 issues - US $ 14 00/Dfl 34.00 including postage 12 issues - US $ 29 50/Dfl 68 00 including postage

Library edition
This will contain the archival material from the personal edition, reprinted and rebound to facilitate storage and retrieval Subscribers to the library edition will also receive a monthly reading room copy of the personal edition

Special introductory offer of 6 + 2 issues - US $ 31 75/Dfl 73 00 including postage 12 + 4 issues - US $ 62 25/Dfl 145 00 including postage

(N.B. the special offer applies to the first six issues only)

Please send your orders or requests for free specimen copies to

In North America - TINS, Elsevier North-Holland Inc , 52 Vanderbilt Avenue, New York, N Y 10017, U S.A
In the U K. - TINS, Elsevier/North-Holland Biomedical Press, 14A Regent Street, Cambridge CB2 1DB, England
The Rest of the World, TINS, P O Box 548, Jan van Galenstraat 335, 1000 AM, Amsterdam, The Netherlands

Brain (1978), **101**, 381-401

BILATERAL TACTILE APHASIA: A TACTO-VERBAL DYSFUNCTION

by MARIE-FRANCE BEAUVOIS, BRIGITTE SAILLANT,
VINCENT MEININGER *and* FRANÇOIS LHERMITTE

(*From the Laboratoire de Neuropsychologie INSERM U 84, Hôpital de la Salpêtrière,
47, Boulevard de l'Hôpital, 75634 Paris Cedex 13*)

INTRODUCTION

FOR nearly a century the existence of a stimulus-specific object-naming defect has been discussed (Freund, 1889). Despite this, the published details of such a defect without others, such as agnosia or asymbolia, are quite rare. Following the first report of optic aphasia by Freund (1889), many cases of visual naming-defects were reported. However, a close analysis of these cases permitted Wolff (1904), followed by Kleist (1916, 1934) to emphasize that in all there was an aphasia or an agnosia, and for this reason, they challenged the use of the term optic aphasia. Until today, except for Freund's case, only two observations may be considered as examples of true optic aphasia (Spreen, Benton and van Allen, 1966; Lhermitte and Beauvois, 1973). With regard to the existence of an auditory anomia, Denes and Semenza (1975) reported the only case of a non-aphasic patient who was unable to name a sound properly but was still able to designate the proper image of the object producing the sound. As for tactile anomia, except for the tactile aphasia of the right hand reported by Raymond and Egger (1906), often claimed to be an astereognosia by many authors (Dejerine, 1906, 1907; Claparède, 1906; Delay, 1935), the only convincing observations of tactile anomia seem to be those concerning left-hand object-naming defects encountered in patients with callosal lesions (Geschwind and Kaplan, 1962; Gazzaniga and Sperry, 1967; Gazzaniga, 1970; Lhermitte, Chain, Chedru and Penet, 1976). If some cases of bilateral astereognosia have been reported (Oppenheim, 1906; Goldstein, 1916; Foix, 1922; Lhermitte and Ajuriaguerra, 1938) we have been unable to find evidence of the existence of bilateral tactile anomia. The only exception seems to be that of Geschwind (1965), who reported an unpublished observation by Kaplan.

The object of this article is to report a case of bilateral tactile aphasia.

CASE REPORT

History

R. G., a right-handed 62-year-old man, without previous symptoms, was found in a state of stupor on March 7, 1974. On examination, a right hemiplegia and probable aphasia were found. Angiography demonstrated in the left hemisphere a parieto-occipital angioma and a hæmatoma without modification of the anterior cerebral artery (fig. 1). The angioma was removed and the hæmatoma evacuated at immediate operation. After three weeks of stupor, clinical examination showed a right hemiplegia with aphasia, both of which regressed rapidly.

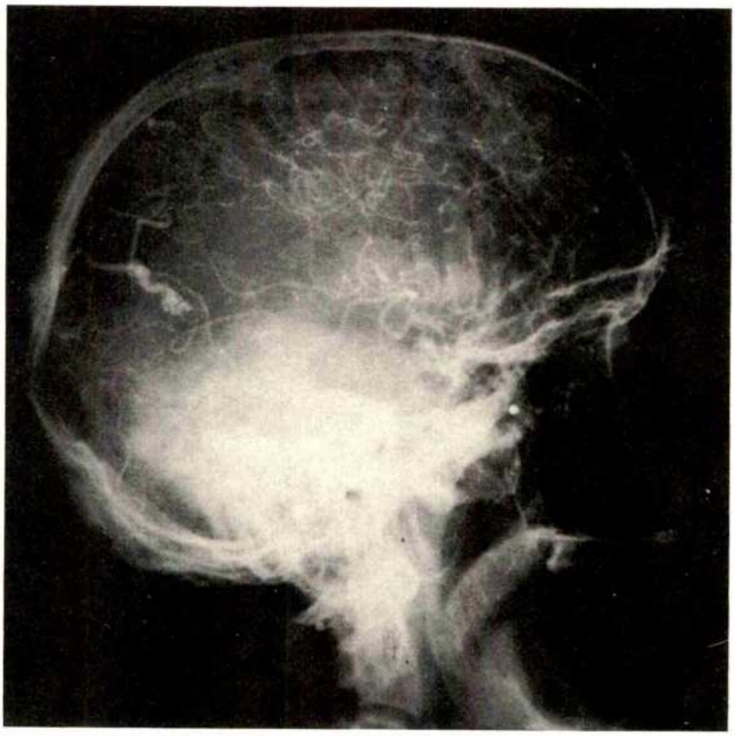


FIG. 1. Left parieto-occipital angioma. Pre-operative angiography.

Between April 1974 and May 1975 the patient lived at home, far from Paris. He was unable to work because of serious reading disability. After one year of unsuccessful re-education, the patient was admitted to Hôpital de la Salpêtrière in May 1975. The chief complaint was not motor or aphasic but reading disability. He was able to write correctly, but he was unable to read what he wrote. He was unable to tell the time, and he complained of difficulties with mathematical calculation and memory. After complete neurological and neuropsychological studies, the patient decided to go home and return to Paris later for re-education. He came back in October 1976, that is, two-and-a-half years after the operation. In October 1976 the neurological and neuropsychological examinations were unchanged from May 1975. Only the latter will therefore be reported.

Neurological Examination (*October 25, 1976*)

The patient complained of no motor or sensory troubles. Walking and standing were correct. Muscular strength and tone were normal, as were the deep tendon reflexes. No Babinski sign was observed. All the following sensory modalities proved to be normal: light touch, pin pinch, hair sensation, temperature, two-point discrimination (thumb, little finger, palm of the hand, big toe), position sense (big toe, hip, thumb, little finger, shoulder), vibration, localization of touch and tests of perceptual rivalry.

Visual acuity was equal to 10/10° (10/10 is normal in the French system) on the right side and 8/10° on the left side (10/10° after correction). The Goldmann test revealed a right inferior quadrantanopia which did not affect the macula. Colour perception tests were normal (Hardy Rand Ritter, Farnworth 100 Hue). The electroencephalogram showed an abnormally slow background activity in the left hemisphere. A left posterior temporo-parieto-rolandic focus of slow waves was constantly observed. Computerized tomography (CT) scans were undertaken on the October 25 1976 with the head scanner of Compagnie Générale de Radiologie. The matrix was 120 × 120, and the scans were parallel to the orbito-meatal line. In the left hemisphere a low density wedge-shaped lesion, with the summit toward the ventricle, was observed on three scans.

Neuropsychological Examination

(1) *Intellectual efficiency*. The patient had worked as an agricultural machinery representative. His intellectual level appeared only slightly diminished, as shown by IQ on WAIS (Verbal IQ 90, Performance IQ 85) and by the 38 Progressive Matrices range (between the 25th and 50th percentiles).

(2) *Calculation*. The patient wrote numbers from dictation correctly; he knew multiplication tables fairly well; he was able to perform mathematical calculation mentally with numbers up to three decimals; he knew and performed mathematical operations correctly and in the correct sequence; he quickly found the solution to verbally proposed problems. Mathematical calculation, however, was abnormal, partly due to his reading troubles, and partly due to difficulties in solving problems with complex data; this last difficulty was typical in other situations (*see later*, comprehension of speech orders). Even though the patient had some difficulties in calculating, one cannot speak of an 'acalculia', since the troubles can be explained by a much more general disturbance of processes which are not specific to calculation.

(3) *Memory*. The patient suffered from some memory disturbances, without serious clinical consequences. However, these troubles dramatically affected learning ability and also disturbed delayed recall. Recall of events before the illness was fairly good, better in content than in their timing. Recall of events after the illness was a little less effective but not sufficient to interfere with daily activity; the recall of dates, however, was much impaired. On immediate retrieval tests (Beauvois and Lhermitte, 1975), the patient achieved a normal score, for each tested modality, auditory-verbal, visual and gestural; but the three learning tests corresponding to these three modalities were impaired. This impairment was also observed for the retrieval of the Rey Complex Figure test and for some subtests of the Wechsler Memory Scale. Therefore, the patient had a normal short-term memory but impairment of memory processing capacity and of middle and long term retention.

(4) *Praxis*. Handling of objects and imitation of using objects without their presence were carried out correctly, either in one hand or in both together. Symbolic acts were also correctly performed. However, imitation of actions without significance was difficult when these actions involved hands, fingers, face and mouth. The patient showed a slight constructional apraxia when he drew a cube, a bicycle, and when he copied the Rey Complex Figure.

(5) *Body Image*. The patient exhibited disturbances in his body image and a finger agnosia, but these disturbances were observed only during verbal tests: he pointed out correctly on himself any part of the body pointed out on the examiner, and conversely; but some mistakes were made when the examiner named a part of the body and asked the patient to point it out, or when the examiner touched a part of the body and asked the patient to name it (either on the patient or on the examiner); these disturbances

are much more consistent with a semantic disorder than with a spatial one (he named the knee instead of the elbow; he called the wrist 'a tibia' and the knee 'an ankle').

(6) *Language Verbal expression.* Spontaneous speech was correct: articulation, intonation and fluency were correct, and sentences were correctly constructed He repeated the 50 syllables, the 125 words and the 10 phrases of the *Examen de l'Aphasie* (Ducarne, 1976) entirely correctly, and all the sentences of the Terman Merill Intelligence Scale at the highest level. Recall of words was precise and quickly performed. He was able to name 50 object-images easily and he quickly stated the opposite of a given word 49 times out of 50. Word definitions were correct (standard score 9 on WAIS Vocabulary Subtest). The patient easily constructed sentences using two or three given words (score 7/7 on the sentences constructing test of *Examen de l'Aphasie*). The patient's verbal expression can therefore be stated as normal.

Understanding of Oral language was fairly good. The patient was able to carry out all the tests of 'oral understanding' of *Examen de l'Aphasie* correctly: pointing out an object named by the examiner (35/35), performing some orders (9/10), and the Three Paper Test of Pierre Marie The critique of irrational stories of the Terman-Merrill Intelligence Scale was correctly performed up to the highest level. A discrimination test on closely-related phonemes (Derouesné and Saillant, 1978) was correctly performed. Semantic discrimination was good (IQ, 98 for the Synonym Test of Binois and Pichot (1958), orally performed). In the orally-performed Token Test (De Renzi and Vignolo, 1962), the four first parts were perfectly performed; however, the results of the fifth part were not good (7/22): this failure seems to be due to difficulty in combining many data and is probably identical to the previously described calculation defects. Therefore, the patient's oral comprehension was correct except for sentences with too much information.

Writing. The patient was able to compose and write a story, to write the names of fifty object images as easily as he could verbally and to take down dictated words and sentences. All these tests were correctly performed except for a moderate dysorthographia; he wrote the words phonetically and incorrectly.

Reading. The patient exhibited a serious reading impairment that will be described in a future publication (Beauvois and Dérouesné, 1978).

(7) *Visual and auditory identification and naming* were normal The patient was able to name 20 different colours and 50 object pictures quickly. He easily recognized the photographs of 48 VIPs The reading impairment was not related to letter recognition defect. The patient was able to recognize and name 15 sounds characteristic of certain objects.

(8) *Naming of objects tactually presented* to either hand was seriously disturbed, whereas the identification of these objects seemed to be correct.

Summary. Two years after the removal of a left parietal angioma the patient exhibited a right inferior quadrantanopia, a mild memory and calculation deficit, a slight constructional and corporeal apraxia, a naming defect of the various parts of the body, an alexia, and a naming defect for objects placed in either hand.

SPECIAL NEUROPSYCHOLOGICAL RESEARCH

This patient who had no expressive or receptive dysphasia and no sensory deficit could not correctly name an object placed in his hand. Experimental research was carried out in order to answer seven questions: (1) was the anomia really specific to the tactile modality? (2) was the anomia different when the object was presented to the left hand or to the right? (3) was the tactile-naming impairment really independent of recognition-impairment (astereognosia)? (4) did the defect appear in the verbo-tactile sense as well as the tacto-verbal sense? (5) was the defect restricted to the naming of objects? (6) was the tacto-verbal impairment dependent on a tacto-visual impairment? (7) could tactile identification be transferred from one hand to the other?

(1) *Was the Anomia Specific to the Tactile Modality*?

In order to test the specificity of the tactile-naming impairment statistically, the performances of this patient in tactile, visual and auditory object-naming were compared. Three comparisons were made: percentages of correct responses, response-naming time, and kind of misnamings.

Naming Tests. The subject was asked to name objects presented to him either tactually (tactile naming), visually (visual naming) or auditorily (auditory naming). For the three kinds of tests the procedure was the same. Stimuli were successively presented during the same testing period. From the time the stimulus was presented to the subject he had one minute to give a response; yet when he named (wrong or right) the object before the end of this period, the next stimulus was immediately presented. We taped the verbal responses and recorded the response times.

Tactile naming. The subject was blindfolded. Fifty objects were placed first in his right hand, then fifty different objects were placed in the other hand, and he was asked to name the objects. One month later the fifty objects which were previously presented to his right hand were presented to his left hand and conversely. The stimuli were everyday objects, for example, tools, food, clothing, etc.

Visual naming. Two kinds of objects were presented. First, in order to allow a direct comparison with tactile naming, the same one-hundred objects previously used for tactile presentation were visually presented. This visual naming test was performed between the two tactile-naming tests, about fifteen days after the first tactile naming. Yet, it might be thought that the difficulty was possibly not equivalent in the visual and tactile naming of the same objects, that is, it was more difficult to name some objects when they were presented to the hand than when presented for visual naming. This is why in a second test, fifty pictures of objects, visually difficult to recognize, were presented to the subject for naming. They were pictures normally used in the neuropsychological laboratory to reveal minor degrees of visual agnosia. For the most part, the objects drawn on the pictures could not be manipulated as they were landscapes, animals and so on.

Auditory naming. Eighty very familiar tape-recorded sounds of objects (telephone bell, cat mewing, bells, etc.) were presented to the patient in a sound-proof room. The patient had to name the object from the sound he heard. It was not possible to find sounds related to the tactually-presented objects, nor to use objects related to recorded sounds for tactile naming. Indeed, objects which can be easily recognized tactually seldom emit a characteristic sound, and many objects which emit a well-known sound cannot be put in the hand (a dog, a bell, an ambulance, a baby crying, etc.). This is why two precautions were taken; first, words corresponding to the sounds used were not more frequent than words corresponding to the tactually-presented objects; secondly, the frequency with which these sounds are heard does not seem higher than the frequency with which the tactually-presented objects are used.

Results. Percentage of correct responses. The sensory modality in which the stimulus was presented (tactile, visual or auditory) had an important effect on the percentage of correct naming responses (tactile-visual comparison: $\chi^2 = 48{\cdot}20$, $P < 0{\cdot}001$; tactile-auditory comparison: $\chi^2 = 25{\cdot}7$, $P < 0{\cdot}001$; visual-auditory comparison: $\chi^2 = 10{\cdot}21$, NS). The patient could correctly name only two objects out of three when these objects were tactually presented, whereas he almost perfectly named objects when they were visually or auditorily presented. Depending on the kind of visual stimulus used, there was a slight difference between performance when the stimuli were pictures (all the responses were correct) and when the stimuli were real objects (four were misnamed).

Mean naming times. Mean naming time was significantly longer for tactually-presented objects (13·8 s) than for auditorily- (6·58 s) or visually- (1·98 s) presented objects. Compared with mean naming time for control subjects, only tactile naming was significantly longer ($F = 227{\cdot}55$, $P < 0{\cdot}001$) than the mean time for normal subjects.

Error analysis. In tactile naming 65 errors were recorded out of 200 responses. Except for some lack of response, some unclassifiable errors, some rare real perseverations and three morphological errors, most of the misnamings (66 per cent) were semantic paraphasias, that is, misnamings which had an obvious semantic relationship with the object's correct name (Table 1). Among these semantic paraphasias, more than half had no morphological relationship with the presented object. For the rest of misnamings, some resemblance to the presented object either in form or in texture could be found; but for all these misnamings the semantic relationship between the stimulus and the misnaming was much closer than the morphological relationship (for example, a cup was named 'a glass', a pair of scissors was called 'a knife', etc.). Therefore, it can be said that most of the misnamings had a semantic relationship with the stimulus.

TABLE 1. SAMPLES OF TACTILE MISNAMINGS

Stimulus	*Response*
a cork	a bottle
a box of matches	some cigarettes
a ladle	a soup-tureen
a glove	slippers
a knife	a fork
a tea-cup	a plate . . . a spoon
a doll	a ball
an old tube of tooth-paste	a worn-out toothbrush

In visual naming, the four recorded misnamings had an obvious semantic relationship with the stimulus. All these misnamings, except one, were immediately and spontaneously rectified by the patient (for a plate, 'a dish . . . sorry . . . a plate'; for an ace bandage, 'a pack of compress bandages . . . no, an ace bandage'; for a strainer 'for serving tea . . . a tea-pot'; for a bowl, 'a cup, no a bowl').

In auditory naming, the only recorded error was an imprecise naming, that is, a sound of a toilet flushing was called 'water'.

(2) *Was the Anomia Different when the Object was Presented to the Left Hand or to the Right Hand*?

In order to test the bilaterality of this deficit we compared the naming performance of each hand: no significant differences were revealed by the comparison of percentages of correct responses, of the response mean times or of the kinds of misnaming (Table 2).

TABLE 2. COMPARISON OF TACTILE NAMING FOR OBJECTS PRESENTED TO EITHER THE RIGHT OR THE LEFT HAND

	Right hand	*Left hand*	
Percentages of correct naming	71%	64%	NS
Mean time for naming	13·9	13·7	NS
Kind of misnamings			
Semantic paraphasias	19	24	NS
Other misnamings	10	12	

NS = not significant.

(3) *Was the Tactile Naming Impairment Really Independent of a Recognition Impairment* (*Astereognosia*)?

Test. Recognition was tested with an 'object-using' test. The patient was blindfolded and asked to show how to use objects placed in his hand by the examiner (either in his right, or in his left hand). The examiner tried in this test, to inhibit the whole verbalization process maximally, explicitly or implicitly. In order to accomplish this, he explained to the subject that if he named the object, he would risk making mistakes, and that he should only think of the tactile sensation when handling the object. To reinforce this attitude, the examiner placed an adhesive tape over the patient's mouth. Forty objects were presented to his right hand and two months later these same forty objects were presented to his left hand.

Results. The subject handled correctly and quickly 79 objects out of the 80 objects presented. Therefore there was a very significant difference between tactile naming and tactile identification performances. These differences were statistically significant, when we compared percentages of correct responses (χ^2: 8·78, $P < 0{\cdot}01$) as well as when we compared response mean times ($t = 6{\cdot}2$, $P < 0{\cdot}001$).

(4) *Did the Defect Appear in the Verbo-tactile Sense as well as in the Tacto-verbal Sense?*

Tests. The examiner spoke the name of an object and at the same time put an object in the patient's hand. The patient had to decide whether the object fitted the stated name. One hundred objects were successively presented (50 to the right hand and 50 to the left). In half the cases, the name spoken by the examiner was the correct name of the object. In the other cases, either (1) there was no relationship between the object presented and the name spoken; or (2) the name spoken fitted an object which had a morphological relationship with the presented object; or (3) the name spoken was semantically related to the name of the object.

Results. The patient made 16 errors out of 100 responses; however, no error was made out of 50 items presented when the correct name was given; thus, the patient only made errors in accepting a false name. If the error percentage was calculated on all the responses, it was comparatively low (16 per cent); but if this percentage was calculated using only the choices with an incorrect proposed word it was 32 per cent, which corresponded exactly to the tactile naming error percentage. Errors did not occur when there was no relationship between the object placed in the hand and the name spoken by the examiner. There were very few errors when the name spoken by the examiner had a morphological relationship with the object presented. Most errors were made when the name of the object spoken by the examiner and the name of the object presented in the hand had an obvious semantic relationship (for example, knife-spoon, ball of wool-reel of thread, alarm-clock-watch, ring-necklet). Therefore, the results of this recognition test were quantitatively and qualitatively identical to those obtained in the tactile naming test.

(5) *Was the Defect Restricted to the Name of the Object?*

In order to test this point, the patient was asked not to state the name of the object, but to explain its use precisely. The results were as follows: 33 per cent of the responses were correct; 20 per cent of the responses were incorrect (for example, having a thimble in his hand he said, 'it's for seamstresses, they thread it inside the thimble. They put it on in order to write . . . or read'); 47 per cent of the responses were along the right lines but were lacking in precision. The patient gave a response which could be applied to a series of related objects (for example, having a spoon in his hand, he said, 'to eat'; for an apple he gave the same response). Thus the defect was not restricted solely to the name of the object, but extended to all responses requiring precise verbal behaviour when presented with a specific object in his hand.

(6) *Did this Tacto-verbal Impairment Result from a Tacto-visual Impairment?*

In order to test this point, two tests were performed.

Tacto-visual matching test. An object was placed in the patient's hand (he could not see it), and at the same time a picture of an object was shown to him. The patient had to decide whether the picture fitted the object in his hand. One hundred objects were successively presented (50 were placed in his right hand, and 50 in his left hand). In one object out of two, the picture fitted the object presented to the hand, though it was usually drawn in a different way (for example, a piece of string was placed in his hand, and at the same time a picture of a ball of string was shown); in the rest of the cases either (a) the picture and the object had no relationship (10 items); or (b) the names of these objects belonged to the same semantic class (plate-spoon; 15 items). In order that testing was tacto-visual and not tacto-verbo-visual, the examiner tried to suggest a non-verbal comparative strategy to the patient.

Results. The 100 responses were correct.

Effect on Tactile Naming of the 'Visual' or 'Tactile' Characteristics of the Objects

The purpose of the following experiment was to compare the patient's tacto-visuo-verbal and tacto-verbal processing. The question was whether visual representation could improve or disturb the naming of tactually presented objects. In order to test this point, we compared tactile naming of two kinds of objects (a) 38 objects thought to be very tactile, i.e. objects where the identification is made almost solely by tacto-kinæsthetic information (weight or texture), the object having no precise form. The objects presented in this test may be classified in 3 categories: flat objects (pieces of paper or cloth); 'string-like' forms (wool, wire); materials usually placed in a pot (water, rice, flour); (b) 38 objects considered to be very visual because they are usually identified visually and even when presented tactually, they need an intermediate visual representation of the object (for example, a chair, a broom); in this test the examiner very strongly suggested a visual representation strategy.

Results. Tactile naming of very visual objects was significantly better than tactile naming of very tactile objects ($\chi^2 = 20{\cdot}73$, $P < 0{\cdot}001$). Compared with the mean percentages in tactile naming, very visual objects were better named ($\chi^2 = 5{\cdot}91$, $P < 0{\cdot}01$); therefore, very tactile objects were not named as well ($\chi^2 = 6{\cdot}72$, $P < 0{\cdot}01$).

(7) *Could Tactile Identification be Transferred from One Hand to the Other?*

The test was the same as the identification test, with only one difference. The object was placed in the left hand and the patient was asked to pretend to use it with his right hand.

Results. Thirty-nine 'usage' gestures out of 40 were correct. Exactly the same result was obtained when the object was placed in the right hand and used with this hand.

ANATOMICAL DATA

Comparison of the Computerized Tomography Scans (CT Scans) with Dejerine's Sections

In spite of numerous atlases already published it was impossible to find one sufficiently precise to furnish a good anatomical analysis of the CT scans. In order to obtain the best estimate the anatomical structures which were probably involved in the lesion, the CT scans were compared with the horizontal sections from Dejerine's book (1895). These sections are nearly parallel to the orbito-meatal line, and are the most precisely described that we could find.

The plane of the first CT scan (fig. 2A) is nearly identical with that of Dejerine's section 48 (fig. 2B). The lesion probably involves the angular gyrus (or pli courbe). Its summit probably does not reach the lateral ventricle. The subcortical fascicles probably involved are the longitudinal inferior fascicle (Fli) and the thalamic radiations (Rth). The plane of the second CT scan (fig. 3A) corresponding to Dejerine's section 52 (fig. 3B), the lesion probably involves the angular gyrus, the longitudinal inferior fascicle, the thalamic radiations (Rth) and the tapetum (Tap.). In the plane of the third CT scan (fig. 4A), corresponding to that of Dejerine's section 56 (fig. 4B), the lesion probably involves the posterior part of the second temporal convolution and the same subcortical fascicles as previously described.

Anatomical Hypothesis

The cortical lesion probably involves the angular gyrus and the posterior part of the second temporal convolution but probably spares the supramarginal gyrus and the anterior part of the second parietal convolution. The subcortical lesion involves essentially what Dejerine calls the 'segment posterieur de la couronne rayonnante' (posterior part of the corona radiata). This segment includes two sagitally directed fascicles—a lateral one, the inferior longitudinal fascicle (Fli) and a medial one, the thalamic radiation (Rth). Besides these, the lesion probably involves the adjacent fascicles, that is, laterally, the vertical occipital fascicle which spreads forward toward the parietal operculum, and a part of the fasciculus arcuatus, while medially it probably involves the tapetum (the occipito-frontal fascicle of Dejerine). In discussing the anatomical pathways involved by the lesion we will only consider anatomical data obtained from human studies. Due to the particular character of the neuropsychological disorder, deriving from a tacto-verbal disorder, we prefer to disregard anatomical data obtained from monkeys.

Connections of the angular gyrus. The intra- or interhemispheric connections of the angular gyrus are not precisely known in Man. Dejerine in his book reports a case of a lesion limited to the angular gyrus and not affecting the subcortical fibres (Case Jouan, Tome II, pp. 122–124), but he does not mention the intra-hemispheric connections. This author suggests, however, other connections of the

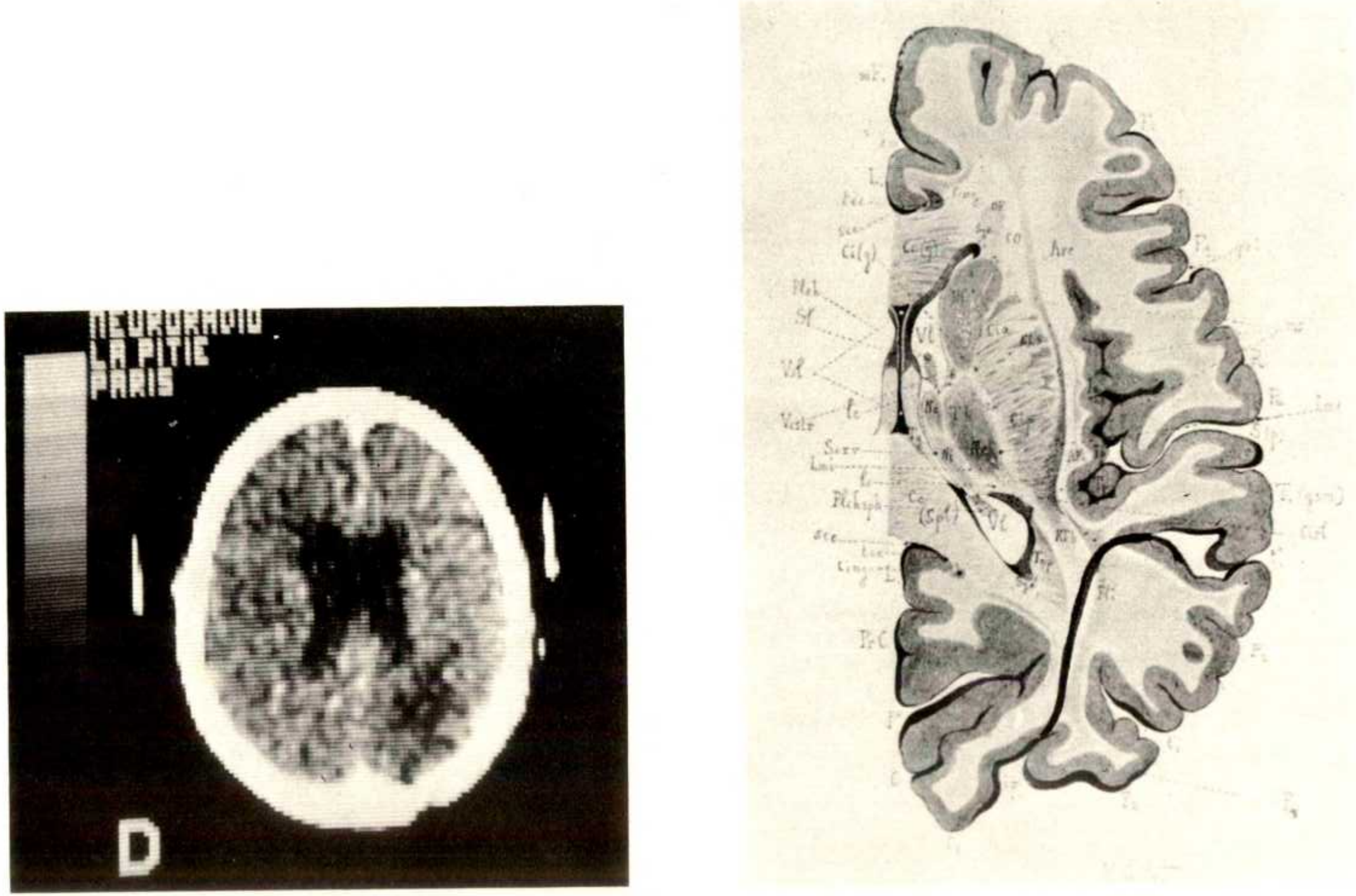


FIG. 2(A) FIG. 2(B)

FIGS. 2–4. Comparison between CT scans and Dejerine's horizontal sections of the brain. For details *see text*. Notice that with the CGR Scan apparatus the left hemisphere is located on the right of the photographs (D indicates the right side).

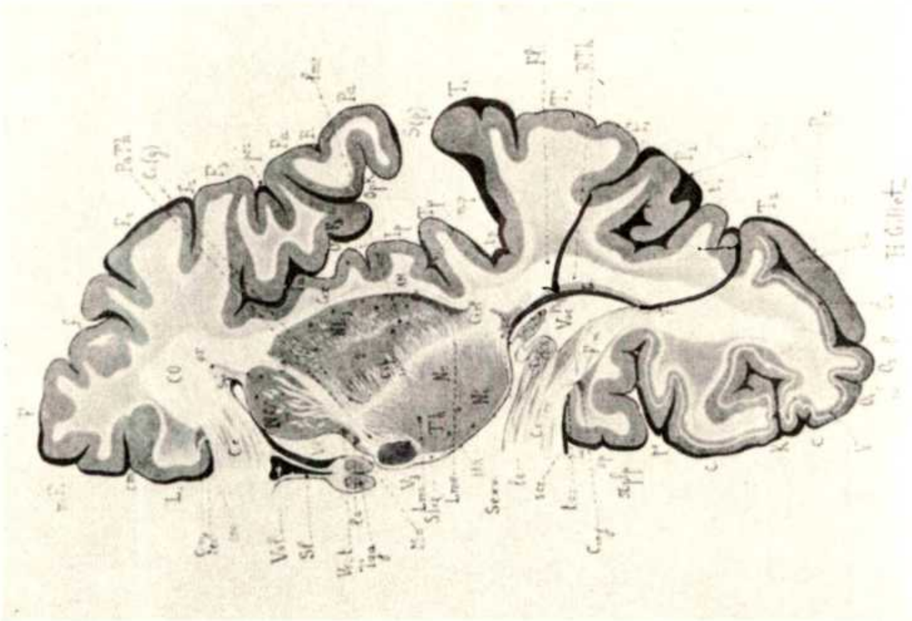


FIG. 3(B)

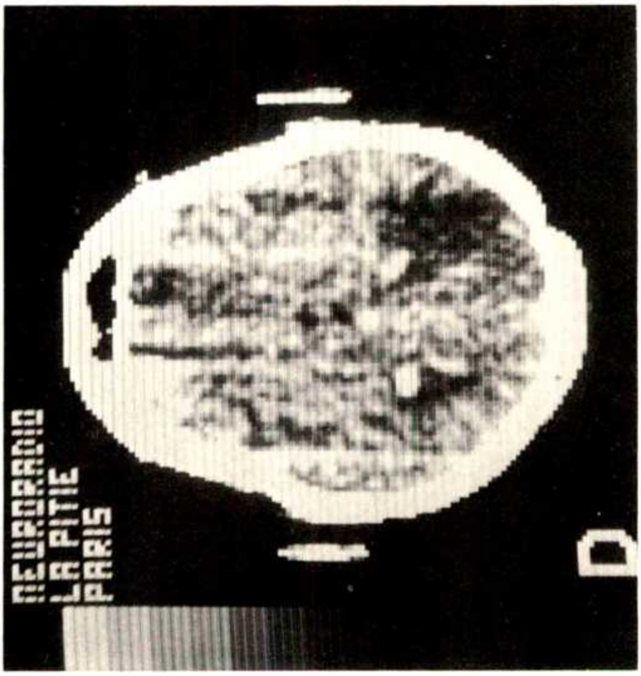


FIG. 3(A)

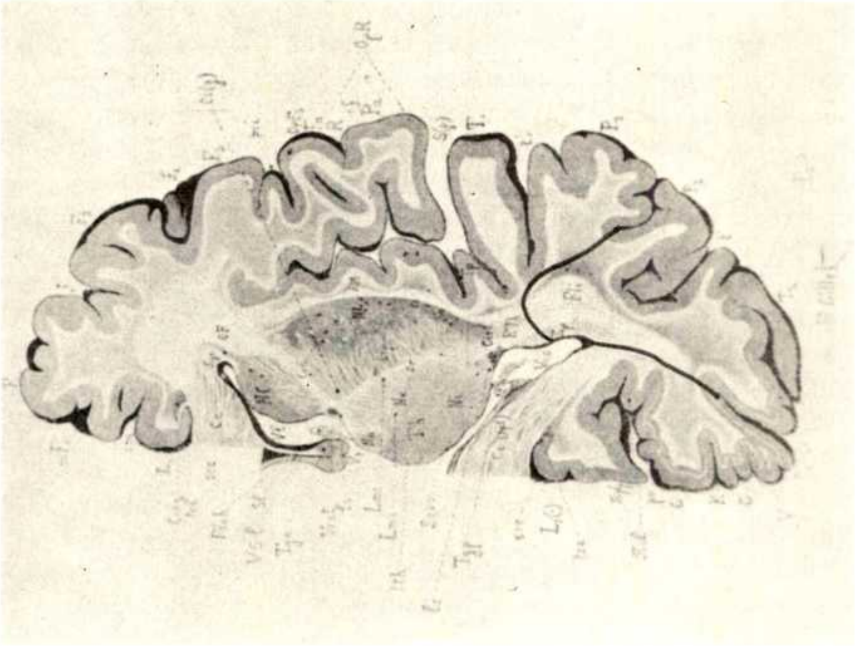


FIG. 4(B)

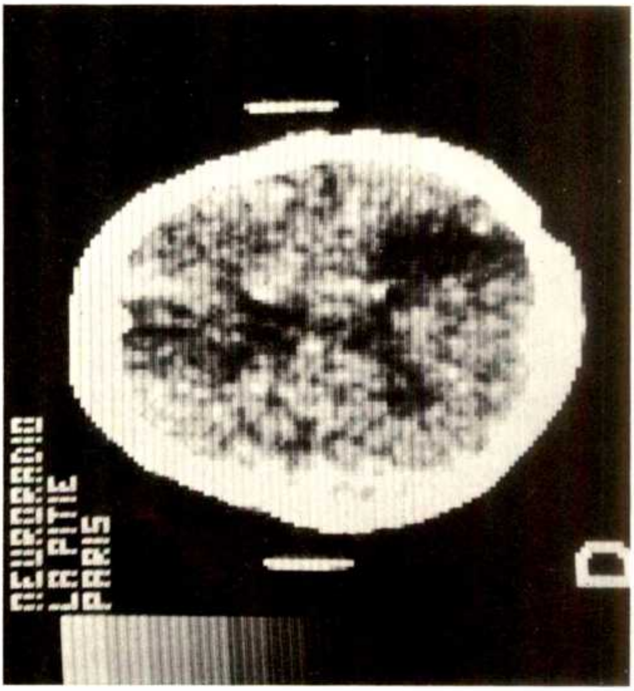


FIG. 4(A)

angular gyrus (Dejerine, Tome I, pp. 756–758). Probably the angular gyrus has connections with the second and third temporal convolutions through some of the vertical fibres of the occipital vertical fascicles. Through short fibres, either U fibres or the fasciculus arcuatus, the angular gyrus has likely connections with further cranial convolutions, such as the supramarginal or the first temporal convolution. However, at the moment it is impossible to define such connections more precisely. As for the interhemispheric connections, the only known ones are the transcallosal fibres to the opposite angular gyrus. However, the exact organization and topography of these fibres is currently unknown, except that they pass through the body of the corpus callosum.

Besides its cortical connections, the angular gyrus has wide connections with certain subcortical nuclei and particularly the thalamus. For Van Buren and Borke (1972) the angular gyrus has a specific relationship with the nucleus dorsocaudalis, and receives the bulk of its afferent fibres from the nucleus pulvinar lateralis.

Fascicles involved in the lesion. Besides the fibres from the angular gyrus, the lesion probably involves other subcortical fascicles. Laterally to medially these are: the longitudinal inferior fascicle, the thalamic radiations and the tapetum. The inferior longitudinal fascicle (ILF) is an occipito-temporal association bundle. Dejerine claims that this bundle connects the occipital cortex (occipital pole lingula, fusiform gyrus, first, second and third occipital convolutions) with the temporal lobe (second and third temporal convolutions, and particularly the first temporal convolution as far as the temporal pole). It is impossible to assert precisely the extent of the lesion of the inferior longitudinal fascicle. It seems likely that fibres from the lingula and fusiform gyri are hardly affected. The tapetum is presumably also involved in the lesion. According to Dejerine (1895) and Vialet (1893), the tapetum does not belong to the corpus callosum, but is an association bundle from the temporo-occipital regions to the frontal lobe (lateral and orbital aspects). However, neither Dejerine (Case Courriere or Case Bras (Tome II, pp. 109, 115)) nor Vialet furnished any details about the exact origin or termination of this bundle. The thalamic radiations are probably also involved, and more particularly the geniculo-calcarine radiation, at least the fibres distributing to the superior lip of the calcarine fissure.

Besides these bundles, we looked for a possible lesion of direct fibres connecting the right parietal lobe to the left temporal lobe. The existence of these fibres is theoretically possible, as most authors have emphasized the fact that the corpus callosum connects various parts of the two hemispheres. If such fibres exist, however, they would pass through the external capsule (Dejerine, 1895) and so would probably be unaffected in our patient.

DISCUSSION

I. (1) The disorder reported here fits the term tactile aphasia, proposed by Raymond and Egger (1906) by analogy with Freund's optic aphasia (1889). Indeed, the two criteria required by most authors (Claparède, 1906; Déjerine, 1906, 1907; Delay, 1935; Geschwind, 1965) to enable us to view a disturbance as tactile modality-specific anomia were found in our patient. First, this patient, in whom no expressive or receptive dysphasia was discovered, misnamed objects when they were presented to him tactually, whereas he almost always gave the correct name when they were presented in a visual or auditory manner; secondly, not only did he have no sensory deficit, but he gave unquestionable proof of ability to identify objects presented tactually (since being blindfolded, he handled perfectly the objects he had failed to name).

(2) Our patient's disorder should be distinguished from a simple tactile anomia, in which only the name of the object is unavailable.

Inability to produce the name of an object was supposed by the associationists to be due to destruction of the association between the image of the object and its name. Others have regarded this inability as due to motor aphasia of a limited kind (Delay, 1935), or as an amnesic aphasia. If these explanations were correct, then (a) the patient should be able to give *verbal* proof that he has succeeded in identifying the object by touch, by describing its morphology or the purposes for which it is used; and (b) his descriptions should be free of dysphasic errors. Our patient, on the contrary, was unable to describe, without making dysphasic errors, the morphology or usage of objects he had correctly identified by touch.

'Tactile anomia' implies the absence of *any* verbal processing when an object is correctly identified by touch. This would be the situation in a split-brain patient who could not produce names for objects placed in his 'non-dominant' hand (see below). Our patient, on the contrary, did not fail to produce names: he produced incorrect names, 66% of which had an obvious semantic relationship with the correct names (semantic paraphasia).

'Tactile anomia' might also imply mere loss of the name of the object. The loss would be remedied if the examiner supplied the name. The patient should always accept the correct name and should always reject false names. Our patient never failed to accept the correct name. His errors were all in accepting false names. He rejected false names which bore no relation to the objects, but accepted many false names which bore some semantic relationship to the objects.

The disorder cannot therefore be thought of as a simple failure to associate the tactile image of an object with its name, or as a simple failure to evoke the correct name of the tactually-presented object. What is really implied is a defect of general tacto-verbal processing. This processing comes into play whenever behaviour necessitates both tactile identification and linguistic processing.

(3) This deficit is not the result of a problem in visual representation of tactually presented objects, as was formerly thought. It is not related to visual, tacto-visual

or visuo-verbal dysfunction. The following points were observed confirming this: tacto-visual matching of objects was perfectly performed; viewed object-naming was almost correctly performed; tactually-presented 'very visual' objects, which may require visual representation as a possible relay, were named much better than 'very tactile' objects, which need no visual representation. These last three results call to mind three important points, (a) in cerebral disease an impairment related to tactile presentation of objects can be observed completely independently of a hypothetical impairment of intermediate visual processing (visual representation). This impairment, specific to the tactile modality, is the equivalent of an optic aphasia for the visual modality; thus, it can be rightly termed tactile aphasia. Concerning this equivalence, it should be noted that manifestations of this impairment are the same in both cases. In the case reported here, as in one case of optic aphasia previously reported (Lhermitte and Beauvois, 1973), misnamings are mostly semantic paraphasias. (b) The fact that such a tacto-verbal dysfunction can be observed in disease, quite independent of an impairment of visual representation, implies that in a normal subject, and at least for certain objects, tactile identification can be processed quite independently of visual identification. (c) The fact that tactually-presented objects are almost always correctly named when they are likely to have a precise visual representation, and the subject is also trained to imagine the object before naming, means that the variable to consider in this dysfunction is *not* the modality of stimulus presentation, but the kind of intermediate processing allowing identification.

(4) How may we account for some rare misnamings (which are also semantic paraphasias) observed when objects were visually-presented? Must we consider that this patient had besides a tactile aphasia a slight optic aphasia? It seems to us to be of great importance that these misnamings appeared only for viewed objects previously tactually presented, that is, objects which can be handled; whereas, misnamings did not appear for pictures of objects which were difficult to perceive and which could neither be handled nor be tactually identified (for example, a slug, a rod etc.). Indeed, it may be assumed that, when searching for the name of the visually-presented object, one sometimes actually thinks of this object in a tactile manner; this must be very rare, but it could be as important as the object being capable of manipulation. If this is true, rare misnamings observed when the objects were visually presented must be considered as consecutive to the tacto-verbal dysfunction, to the tactile aphasia. This hypothesis could account for the low percentage of misnamings observed in all modalities in other cases of specific aphasias (Spreen *et al.*, 1966; Lhermitte and Beauvois, 1973).

II. With the exception of cases of unilateral left-hand anomias in split-brain patients (Geschwind and Kaplan, 1962; Gazzaniga, 1970) observations of tactile aphasia or anomia are rare. Two explanations are possible. Either cases of bilateral tactile anomia exist more frequently and have not been sought effectively, or bilateral tactile anomia or aphasia is really uncommon, the lesion or the association of lesions causing it being rare in cerebral disease states. At the moment it is not possible to reach a conclusion on the second possibility, but it is very likely that tactile aphasia may be missed if incorrectly sought for. Indeed, this study implies two methodological precautions which do not seem to have been taken into account: (a) a systematic study should be made of the naming ability in relation to each sensory modality in any patient having a cerebral lesion, and not only in aphasic patients. The only systematic studies concerning naming ability have been performed in aphasic patients (Spreen *et al.*, 1966; Goodglass, Barton and Kaplan, 1968); (b) a second precaution should be taken when seeking a naming impairment restricted to the tactile modality, namely to establish that this impairment is due neither to sensory deficit nor to defect of tactile identification (astereognosia). It is because this last criterion was not taken into account that the previously reported case of Raymond and Egger was not recognized as tactile aphasia. Conversely, it is possible that among cases of bilateral astereognosia reported by Foix (1922) there were examples of tactile anomias. Indeed, the authors did not distinguish, by non-verbal tests, identification impairment from a possible naming impairment.

The problem, however, is not only that these two points have not been taken into account in systematic studies nor in particular case reports. Distinguishing identification from naming requires that the implicit part of language in every test be taken into account in order to exclude verbalization in an identification test. Therefore, when a patient is asked to give the name of an object, if he fails to say or to show how this object is used, a verbal searching-strategy is first induced. If verbalization is not destroyed but only disturbed, this can then lead to mistakes in an identification test. This was the case with our patient when we did not inhibit verbalization (he made a semantic 'parapraxia' when using an object; for instance he used a toothbrush like a comb). This is why we inhibited verbalization by special instructions in every identification test in a second series of tests, so that we could be sure that we were testing identification and not the consequences of implicit misnaming.

III. The bilaterality of the disturbance in this case is of great interest. Is the infrequency of such an observation related to the association of two different disturbances, a naming impairment for the objects presented to the right hand, plus a naming impairment for the objects presented to the left hand or is it a single impairment? The answer to this question may help in conceiving processes of both object-identification and naming in normal subjects, and in stating at what level information coming from the right hand or the left hand are separately processed.

At first sight our results seem to favour a single disturbance, but these results are not conclusive: (a) results in the naming test are exactly the same when objects are presented to the right hand as when they are presented to the left hand; this is true quantitatively as well as qualitatively; but this does not mean the reason is the same in both cases; (b) tactile information can be transferred from one hand to the other, since the patient can pretend to use with his right hand an object put in his left hand. There is no evidence that this transfer is necessarily effected when the patient is asked to name an object; (c) anatomically, it seems that one region alone is involved by the lesion; it is well-known that a single lesion can destroy the anatomical substrate of a number of functional systems.

In order to answer our problem we have to consider other reported cases of tactile naming impairment. Unfortunately the only ones known are unilateral left tactile anomias following section or lesion of the corpus callosum (Geschwind and Kaplan, 1962; Gazzaniga and Sperry, 1967; Gazzaniga, 1970; Lhermitte *et al.*, 1976; Lhermitte, Marteau, Serdaru and Chedru, 1977). Split-brain patients are able to give proof of tactile identification processing for objects held in their left hand (which cannot be named) as well as for objects held in their right hand. At first sight this appears to demonstrate that there are indeed two independent systems for tactile identification: one for the left hand and one for the right hand, one having its anatomical basis in the right hemisphere and the other in the left hemisphere. If this is the case, the bilateral tactile aphasia reported here could be explained only by the connection of two disturbances (this does not mean, of course, that these systems are not connected in normal subjects).

However, the tactile naming behaviours of split-brain patients, and of our patient, and the kind of identification proof that can be obtained in both cases are very different. The conventional ways used to test identification in split-brain patients (handling objects, drawing objects or selecting one similar object among several) give proof of a high level of perception, but between this kind of identification and object-naming, a more categorical or pre-naming processing is necessarily implied (for instance, this pre-naming linguistic processing is necessary to sort objects into semantic categories). In the case reported here, this processing is indeed carried out since most errors are semantic paraphasias. This does not seem to obtain for the left hand of split-brain patients; it seems that when objects are presented to their left hand, split-brain patients can make no verbal response or can utter only names unconnected with the objects presented.

The following conclusions can be drawn from comparison of these two kinds of results: (1) split-brain patients' results in the tactile identification test prove that in normal subjects a first level, a presumably non-linguistic one, is processed separately for each hand; (2) our patient's results in tactile-naming prove there is an intermediate process of semantic sorting between this first identification level and precise object-naming. The question is whether this level is processed separately for each hand or not. At the present time, it is impossible to state whether this semantic sorting is separately processed for each hand or not.

IV. In spite of numerous uncertainties the anatomo-functional implications of our case must be considered.

Before stating any anatomo-functional hypothesis, two points have to be taken into account: what are the precise psychological data on one side and anatomical data on the other, in the case studied? What are the functional postulates which can reasonably be stated from classical anatomo-pathological data and from human experimental data? In our patient, there are two main anatomical facts: there are no arguments for a lesion of the right hemisphere or of the corpus callosum; the lesion involved the parietal lobe and its intra-hemispheric connections, and also some connections of the occipital lobe with the frontal or temporal lobe of the same side. Two major anatomo-functional postulates proceed from classical anatomo-pathological data and from some human experimental information: linguistic processings are undertaken by the left temporal region, while tactile identification processings are undertaken by the parietal lobe, most probably by the region caudal to the post-central convolution. We may conclude from this that the defect reported here is probably related to involvement of the cortical and subcortical structures located between these two regions. However, the problem is different if the bilateral tactile aphasia results from one or two types of disturbance. If the tactile aphasia of the right hand results from a different disturbance from the tactile aphasia of the left hand, the tactile aphasia of the right hand could be due either to involvement of the connections of the left superior and inferior parietal lobules or, less probably, to involvement of the left angular gyrus and/or its connections to the temporal lobe (U fibres or fasciculus arcuatus). The tactile aphasia of the left hand could result from the involvement of the fibres from the right parietal lobe after these have relayed in the left superior and inferior parietal lobules. If the tactile aphasia results from a simple disturbance the only one lesion which could explain it is involvement of the left angular gyrus. Comparison with other cases of tactile aphasia with slightly different lesions would permit a choice between these different solutions.

SUMMARY

Bilateral tactile aphasia was exhibited by a patient who was operated upon for a left parieto-occipital hæmatoma. Neuropsychological investigation established the following points: (1) the patient, in whom no expressive or receptive dysphasia could be found, misnamed objects when they were presented to him tactually, whereas he almost always gave the correct name when they were presented visually or auditorily; (2) the naming disturbance was identical when the object was presented to the left hand or to the right hand; (3) not only did the patient have no sensory deficit, but he could give unquestionable proof of correct tactile identification by using the objects presented to him tactually; (4) the defect appeared in the verbo-tactile as well as in the tacto-verbal direction; (5) it was not restricted to the name of the object since the patient was unable to describe, without making dysphasic errors, the morphology or usage of objects presented to him tactually; (6) the tacto-verbal dysfunction did not result from a tacto-visual impairment. Computerized tomography scans showed that: (1) there was no evidence suggesting a lesion of the right hemisphere, nor of the corpus callosum; (2) the left lesion

involved the angular gyrus, the posterior part of the second temporal convolution, the inferior longitudinal fasciculus, the geniculostriate fibres and some fibres of the tapetum.

ACKNOWLEDGEMENTS

We thank Professor Metzger who provided the CT scans, Professor Dérouesné who permitted us to examine his patient and Denise Binet who tested the patient's ability to calculate.

REFERENCES

BEAUVOIS, M. F and DÉROUESNÉ, J. (1978) Analytic alexia—three dissociations. In preparation.

—— and LHERMITTE, F. (1975) Déficits mnésiques électifs et lésions corticales restreintes. *Revue Neurologique*, **131**, 3–22.

BINOIS, R. and PICHOT, P. (1958) *Test de Vocabulaire*. Paris: Editions du Centre de Psychologie Appliquée, p. 16.

CLAPARÈDE, E. (1906) Agnosie et asymbolie; à propos d'un soï-disant cas d'aphasie tactile. *Revue Neurologique*, **14**, 803–805.

DEJERINE, J. (1895) *Anatomie des Centres Nerveux*. Paris: Rueff, Vol. 1, p. 816; Vol. 2, p. 720.

—— (1906) Considérations sur la soi-disant 'Aphasie tactile'. *Revue Neurologique*, **14**, 597–601.

—— (1907) A propos de l'agnosie tactile. *Revue Neurologique*, **15**, 781–784.

DELAY, J. (1935) *Les Astéréognosies*. Paris: Masson, p. 548.

DENES, G. and SEMENZA, C. (1975) Auditory modality-specific anomia: evidence from a case of pure word deafness. *Cortex*, **11**, 401–411.

DE RENZI, E. and VIGNOLO, L. A. (1962) The Token Test: a sensitive test to detect receptive disturbances in aphasics. *Brain*, **85**, 665–678.

DÉROUESNÉ, J. and SAILLANT, B. (1978) Composante articulatoire dans la comprehension des phonèmes. (In preparation.)

DUCARNE, B. (1976) *Test pour l'Examen de l'Aphasie*. Paris: Editions du Centre de Psychologie Appliquée.

FOIX, C. (1922) Sur une variété de troubles bilatéraux de la sensibilité par lésion unilatérale du cerveau. *Revue Neurologique*, **29**, 322–331.

FREUND, D. C. (1889) Ueber optische Aphasie und Seelenblindheit. *Archiv für Psychiatrie and Nervenkrankheiten*, **20**, 276–297, 371–416.

GAZZANIGA, M. S. (1970) *The Bisected Brain*. New York: Meredith Corporation, p. 172.

—— and SPERRY, R. W. (1967) Language after section of the cerebral commissures. *Brain*, **90**, 131–148.

GESCHWIND, N. (1965) Disconnexion syndromes in animals and man. *Brain*, **88**, 237–294, 585–644.

—— and KAPLAN, E. (1962) A human cerebral deconnection syndrome. *Neurology, Minneapolis*, **12**, 675–685.

Goldstein, K. (1916) Über Kortikale Sensibilitäts Störungen. *Neurologie Zentralblatt*, **19**, 825–827.

Goodglass, H., Barton, M. I. and Kaplan, E. F. (1968) Sensory modality and object-naming in aphasia. *Journal of Speech and Hearing Research*, **11**, 488–496.

Kleist, K. (1916) Über Leitungsaphasie und grammatische Störungen. *Monatsschrift für Psychiatrie und Neurologie*, **40**, 118–199.

—— (1934) Kriegsverletzungen des Gehirns in ihrer Bedeutung für die Hirnlokalisation und Hirnpathologie. In: *Handbuch der ärztlichen Erfahrungen im Weltkriege 1914–1918*. Edited by O. von Schjerning. Leipzig: Barth, Vol. IV.

Lhermitte, J. and Ajuriaguerra, J. de (1938) Asymbolie tactile et hallucinations du toucher. Étude anatomo-clinique. *Revue Neurologique*, **70**, 492–495.

Lhermitte, F. and Beauvois, M. F. (1973) A visual-speech disconnexion syndrome. *Brain*, **96**, 695–714.

—— Chain, F., Chedru, F. and Penet, C. (1976) A study of visual processes in a case of interhemispheric disconnexion. *Journal of Neurological Sciences*, **28**, 317–330.

—— Marteau, R., Serdaru, M. and Chedru, F. (1977) Signs of interhemispheric disconnection in Marchiafava Bignami Disease. *Archives of Neurology*, **34**, 254.

Oppenheim, H. (1906) Über einen bemerkenswerten Fall von Tumor cerebri. *Berliner Klinische Wochenschrift*, **43**, 1001–1004.

Raymond, F. and Egger, M. (1906) Un cas d'aphasie tactile. *Revue Neurologique*, **14**, 371–375.

Spreen, O., Benton, A. L. and van Allen, M. W. (1966) Dissociation of visual and tactile naming in amnesic aphasia. *Neurology, Minneapolis*, **16**, 807–814.

Van Buren, J. M. and Borke, R. C. (1972) *The Nuclei and Cerebral Connection of the Human Thalamus*. Heidelberg: Springer-Verlag, Vol. 1, p. 471.

Vialet, N. (1893) *Les Centres Cérébraux de la Vision*. Paris: Alcan, p. 351.

Wolff, G. (1904) *Klinische und kritische Beiträge zur Lehre von den Sprachstörunger*. Leipzig: Veit.

(*Received July 19, 1977*)

COLLEGE LIBRARY

Bram (1978), 101, 403–445

THE NEUROANATOMY OF AMNESIA

A CRITIQUE OF THE HIPPOCAMPAL MEMORY HYPOTHESIS

by JAMES A. HOREL

(*From the Department of Anatomy, SUNY, Upstate Medical Center, Syracuse, New York 13210, USA*)

INTRODUCTION

THE HIPPOCAMPUS has had a spectacular and controversial history. It was once related to the olfactory system, then to emotional functions, and finally has settled into a career as an organ of learning and memory, supported in this role by a complex structure of frequently contradictory and controversial evidence. Our research on the temporal lobe has caused us to question the interpretation of evidence that is central to the hippocampal memory hypothesis and to propose an alternative interpretation. This has required a re-examination of the entire structure that supports this hypothesis. I present here the results of that examination.

The Problem

Bilateral destruction in the medial area of the temporal lobe in humans produces a severe amnestic syndrome with a permanent anterograde amnesia and a retrograde amnesia for a short period prior to the injury (Scoville, 1954; Scoville and Milner, 1957; Penfield and Milner, 1958). Early memories and memories for technical skills remain intact and there is no loss of general intelligence or complex perceptual abilities (Scoville and Milner, 1957). Scoville and Milner (1957) found that when removals of the medial temporal lobe included only the uncus and amygdala there was no amnesia, but when the lesion extended far enough posteriorly to include the hippocampus the memory defect occurred and its severity appeared to depend upon the posterior extent of the lesion. From this, they proposed that the memory impairment was due to hippocampal damage, a conclusion which obtained further support from studies of the pathology of Korsakoff's disease and posterior cerebral artery occlusion. One of the major connections of the hippocampus is to the mammillary bodies by way of the fornix and there is a high incidence of mammillary body disease in amnestics with Korsakoff's psychosis (Malamud and Skillicorn, 1956; Barbizet, 1963; Victor, Adams and Collins, 1971). Also, medial temporal lesions that result from posterior cerebral artery occlusion sometimes produce memory defects and one of the structures consistently injured in such cases is the hippocampus (*see* Glees and Griffith, 1952; Victor, Angovine, Mancall and Fisher, 1961).

For these and other reasons, it has now become generally accepted that medial temporal lesions produce their memory defects by destruction of the hippocampus. However, there has been an awkward problem with this theory. Given the extreme severity of the impairment and its rather general character, one would certainly have anticipated that hippocampal lesions in animals would produce obvious deficits in learning and memory. The results of such lesions have not confirmed this anticipation. I will summarize this massive and controversial literature by quoting from the reviews of three authorities on the subject.

Douglas (1967) said that 'Hippocampal lesions do not impair learning in general, even when the learning involves retention for a long period of time. Thus the animal and human data would appear to be in contradiction'. Douglas then went on to theorize that the memory defect in man '. . . is a secondary effect of a different type of primary disorder'. Kimble (1968) stated 'Although much of the research on the hippocampus was prompted by the reports of Scoville (1954) and others . . . in which bilateral hippocampal damage produced severe anterograde amnesia, the experimental literature fails to support such an interpretation for the dozens of animal studies now completed'. Kimble then proposed that the hippocampus is involved in Pavlovian internal inhibition. Finally, Isaacson (1972) said 'Turning to the experimental literature with animals, the data from the overwhelming majority of experiments fail to connect bilateral destruction of the hippocampus with any apparent recent memory loss'. He then went on to suggest that the deficit in man is due to the original epileptic disorder that led to the surgery.

The Solution

The apparent lack of correspondence between the results of human and animal hippocampal lesions creates a major barrier to our ability to study this important problem experimentally and has motivated a number of theories to account for the discrepancy. Man and animals are undeniably different and one suggestion is that this is just another expression of that difference. A far more popular argument has been that we simply have not used tests with animals that are comparable to the ones by which we recognize these memory defects in people (*see* Gaffan, 1974; Iversen, 1976). Neither of these arguments has been particularly compelling. The phylogenetically conservative hippocampus seems an unlikely place to expect radical changes in function, and from the severity of the human memory defect, we would not anticipate that the results of animal hippocampal destruction would be so subtle as to require very special tasks to detect them. A rarely explored alternative is that the amnesia produced by medial temporal lobe lesions is not due to hippocampal damage at all but to some other structure that is also injured by these lesions. We have been studying the temporal lobe of monkeys by examining the behavioural effects of disconnecting it from other structures of the brain (Horel and Keating, 1969, 1972; Keating and Horel, 1971, 1972; Horel and Misantone, 1974, 1976; Horel, Keating and Misantone, 1975). In two of these experiments (Horel and Misantone, 1974, 1976) we cut part of the white matter medial to the temporal lobe; an area which has been called the temporal stem, or albal stalk (TS, fig. 1). It is white matter that contains connections of afferents and efferents of temporal cortex and amygdala, but carries no connections of the hippocampus.

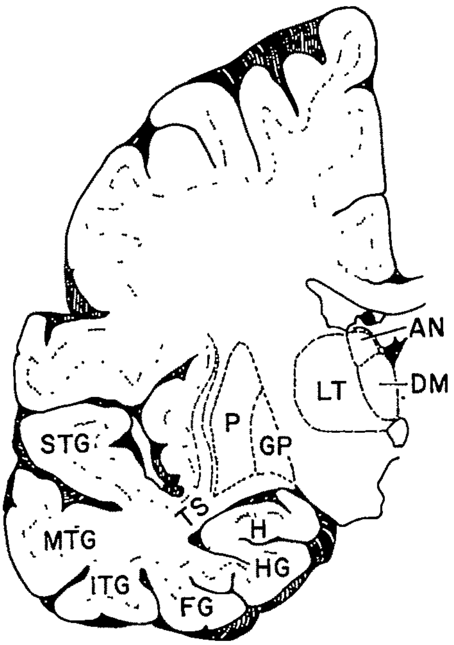


FIG. 1. The hippocampus and the temporal stem. AN = anterior nuclear group; DM = dorsomedial nucleus, FG = fusiform gyrus; GP = globus pallidus; H = hippocampus; HG = hippocampal gyrus; ITG = inferior temporal gyrus, LT = lateral thalamus; MTG = middle temporal gyrus; P = putamen; STG = superior temporal gyrus; TS = temporal stem.

These relatively small lesions abolished the ability of the animals to relearn a visual pattern discrimination that they had readily learned pre-operatively. We noted that with the anterior approach used by Scoville (Scoville *et al.*, 1951; Scoville and Milner, 1957) at least some of this white matter would have had to have been cut in the medial temporal lobectomy of the human patients. Also, the further the lesion extended posteriorly, the greater the likelihood that the closely adjacent temporal stem would be involved. We suggested that perhaps the amnestic syndrome that results from these medial temporal removals in humans was due to cutting some of the fibre connections of the temporal cortex which are contained within the stem rather than to hippocampal damage.

This caused us to re-examine the literature that bears upon the neuroanatomy of amnestic syndromes. It soon became apparent that this literature has consistently been reviewed with an eye toward bending it into agreement with the hippocampal memory hypothesis. We found that not all of the evidence supports this hypothesis and there are alternative explanations for the evidence which does appear to support it that are at least as plausible. In fact, the argument of this paper is that there is good reason to believe that the hippocampus-fornix-mammillary body system is not responsible for the memory defects characteristic of medial temporal lesions or of Korsakoff's psychosis. This evidence and an alternative system are presented in the following paragraphs.

In this paper we are not looking for the site in the brain where learning and memory takes place, nor the location of engrams or memory traces. We are attempting to discover the structures of the brain whose damage produce certain well-known symptoms, often called the amnestic syndrome. Whether or not a location can be found for memories, symptoms of memory disorder can be produced by fairly limited lesions. Here we are tracking the anatomy of symptoms of memory disorder, not the anatomy of memory.

The Human Hippocampus and Memory

The principal source of evidence. The assertion that memory disorders result from hippocampal lesions derives its support principally from the effects of human medial temporal lobe lesions. The reports that form the foundation for the hippocampal memory hypothesis are those of Scoville (1954), Scoville and Milner (1957) and Penfield and Milner (1958). The memory defects that are a consequence of this surgery are well-known and the data are frequently reviewed (*see* Milner, 1972). However, it is important for present purposes to recall the severity of the defect; to that end I include here a brief description of the most famous case, that of H. M.

Scoville and Milner describe H. M. in the following manner: 'After operation this young man could no longer recognize the hospital staff, nor find his way to the bathroom and he seemed to recall nothing of the day-to-day events of his hospital life. There was also a partial retrograde amnesia inasmuch as he did not remember the death of a favourite uncle three years previously, nor anything of the period in the hospital, yet could recall some trivial events that had occurred just before his admission to the hospital. His early memories were apparently vivid and intact'. To illustrate his defect, the authors wrote: 'Ten months ago the family moved from their old house to a new one a few blocks away on the same street; he still has not learned the new address, though remembering the old one perfectly, nor can he be trusted to find his way home alone. Moreover, he does not know where objects in continual use are kept; for example, his mother still has to tell him where to find the lawn mower, even though he may have been using it only the day before. She also states that he will do the same jigsaw puzzles day after day without showing any practice effect and that he will read the same magazines over and over again without finding their contents familiar'. These observations of severe impairment were confirmed with formal testing.

This same operation was also performed on psychotic patients but because of their debilitating behaviour disorder, the memory defect went unnoticed until the case of H. M. brought it to attention. It is apparent, however, that a defect of this magnitude would not, under ordinary circumstances, go undetected by even the most casual observer. Furthermore, we would not, *a priori*, anticipate that if these lesions were reproduced in animals the defect would be subtle and difficult to detect or appear only in a few restricted tests of learning and memory.

It is also important to notice that although the memory defect is extremely severe, some learning can take place (Milner, Corkin and Teuber, 1968). H. M. can acquire some motor tasks and could learn a tactual maze in which the sequence of turns fits into his immediate memory span. He had difficulty in learning this simple maze and was unable to learn a more complex maze that is easily learned by normal subjects. Immediate memory, such as the ability to repeat back a string of digits, remains unimpaired in these patients. However, in the tasks he could learn, H. M. was severely impaired in his rate of acquisition. These vestigial learning skills had parallels in his everyday life. 'He seems to have learned something about the constant features of his environment such as the general arrangement of rooms and furniture in his home. He also occasionally appears to remember some outstanding personal or public event, though with little constancy from day to day'. (Milner *et al.*, 1968).

Scoville made his medial temporal lesions by approaching from the anterior end of the temporal lobe and extending the lesions posteriorly in varying amounts (Scoville and Milner, 1957). If the lesion included only the uncus and amygdala there was no memory impairment. If the lesion extended far enough posteriorly to include the hippocampus, the memory defect appeared and the further posteriorly the lesion extended the worse the impairment. This led to the interpretation that the amnesia was caused by the hippocampal lesions.

In the next section we examine the cognitive functions of the monkey's temporal cortex and attempt to determine if symptoms of learning and memory disorder might be related more to one structure than another.

Cognitive Deficits With Temporal Lobe Lesions

The Klüver–Bucy syndrome. The introduction to the cognitive nature of deficits that result from temporal lobe lesions in monkeys was made by Klüver and Bucy (1938, 1939). The same observations made earlier by Brown and Schafer (1888) had gone unnoticed. They found that bilateral temporal lobectomy in monkeys produced a remarkable behavioural effect: (1) a symptom that has sometimes been called 'psychic blindness' or 'visual agnosia' in which the animals seem unable to use vision to differentiate the significance of objects. For example, they seem unable to differentiate between things that are edible and things that are inedible until they are placed in the mouth; (2) 'oral tendencies'. The animals continually examine all objects in reach by mouth, (3) 'hypermetamorphosis', described as 'an excessive tendency to take notice and to attend and react to every visual stimulus', (4) emotionality changes in which the animals show '. . . either profound changes in emotional behaviour or complete absence of all emotional reactions in the sense that the motor and vocal reactions generally associated with anger and fear are not exhibited', (5) an increase in the occurrence and diversity of sexual activity.

It has been suggested that the first symptom listed above is responsible for all the rest (Geschwind, 1965). Thus, the temporal-lobectomized monkey is unable to use vision to decide whether to eat an object, or ignore it, flee from it, attack it or copulate with it. This suggestion is supported by the finding that disconnecting the occipital and temporal lobes produces most of the Klüver-Bucy symptoms (Downer, 1961; Horel and Keating, 1969, 1972). We did this by destroying one temporal lobe, the contralateral occipital lobe, and cutting the splenium of the corpus callosum. No single one nor two of these lesions produced the deficit, but, all three which together should have cut off visual information from the remaining temporal lobe did produce the Klüver-Bucy syndrome (Horel and Keating, 1969, 1972). Emotional reactions could be elicited, but not by visual stimuli in the animals with occipitotemporal disconnection. Our animals seemed totally bewildered by many simple tasks they had performed repeatedly pre-operatively; they behaved as though they had never encountered them before.

We found that although 'disconnection' and 'bitemporal' animals are unable at first to distinguish between food and nonfood objects (for example, raisins and steel bolts) that are placed before them, they eventually re-acquire this ability if given practice. However, this learning does not transfer to another pair of food and junk objects. The monkeys had to learn to differentiate each new pair of objects on which we tested them. Once having learned these simple differentiations which a normal animal makes instantly, their subsequent retention of the task was excellent. It seemed to us that the general behaviour of bitemporal and disconnection animals suggested a lack of recall for visual experience of even the most elementary sort.

Terzian and Orre (1955) observed very nearly the same symptoms which were described by Klüver and Bucy in a patient with a bilateral temporal lobectomy that included the temporal cortex, uncus, amygdala, hippocampus and hippocampal gyrus. Post-operatively the patient exhibited abnormal sexual behaviour (exhibitionism, homosexuality), hypermetamorphosis, an inability to recognize even close relatives and a complete absence of emotional behaviour. The patient's speech was unaltered in its elaboration and pronunciation, but 'his language had become poorer and was composed of very elementary sentences within the limits of his natural needs, concerning the present and without reference to the past'. He also appeared to have a serious memory problem: 'Not only did he not remember at all what had recently happened, he did not remember anything of his past. Even when we insisted on knowing something about his house, his family, the city he lived in, the patient did not even seem to understand these questions, as if their object was entirely unknown to him. It was not possible to analyse his memory functions, but we can affirm that the patient felt completely isolated, without a past to remember and consequently without any future whatever'.

Localization of symptoms of temporal lobe injury. Terzian and Orre felt that their patient behaved much like Klüver and Bucy's monkeys. The Klüver-Bucy syndrome is a complex emotional and cognitive disorder that results from removal of a diverse collection of structures roughly subsumed under the rubric of temporal lobe. A certain amount of dissection of the symptoms with selected lesions has been possible in animal experiments and has led to the conclusion that the cortex of the middle and inferior temporal gyri (generally called the 'inferotemporal cortex') is the source of the 'psychic blindness'. Lesions here produce severe deficits in the learning and retention of visual discriminations, but destruction of the hippocampus or amygdala does not (Mishkin, 1954; Mishkin and Pribram, 1954). Simple visual tasks (that is, tasks that can be learned in relatively few trials) are disturbed less and sometimes not at all by inferotemporal lesions (*see* Mishkin, 1954; Mishkin and Pribram, 1954; Mishkin and Hall, 1955). These visual deficits cannot be accounted for by changes in visual acuity (Weiskrantz and Cowey, 1963). The effects of inferotemporal lesions are restricted to the visual modality (reviewed by Mishkin, 1966; Gross, 1972).

Recently, functional differences between the anterior and posterior parts of the inferotemporal cortex have emerged (Iwai and Mishkin, 1968; Cowey and Gross, 1970; Delacour, 1977). Posterior lesions produce deficits that have been characterized as perceptual in which the deficit depends upon the nature of the discriminanda (Gross, Cowey and Manning, 1971). Anterior lesions produce deficits that are described as 'mnemonic' or 'associative' in nature; animals with such lesions appear to have deficits in forming stimulus-reinforcement associations (Jones and Mishkin, 1972, described below). Deficits in auditory discrimination follow removal of the superior temporal gyrus (*see* Iversen and Mishkin, 1973).

The anterior end of the temporal lobe appears to be multimodal in its function (Stamm and Rosen, 1971; Jones and Mishkin, 1972). Jones and Mishkin studied the effects of lesions to the anterior end of the temporal lobe, to the orbital cortex (which connects to the temporal lobe by the uncinate fasciculus) and to the hippocampus on object and place reversal problems. On the object reversal, the animal is trained to discriminate between two objects. After the animal has reached criterion the object that was rewarded now becomes the unrewarded object and the animal then learns the reverse of the original discrimination. This switch is repeated several times. The place reversal task is basically the same except that instead of the reward being linked to an object, it is related to the position of the stimulus. At first only the left side is rewarded and after that is learned, then the correct position is switched and only the right side is rewarded and so on. The number of trials to learn the reversals is taken as a measure of stimulus-reward association. Animals with anterior temporal lesions and those with frontal orbital cortex lesions are severely impaired on the object reversal but animals in which the hippocampal gyrus and the hippocampus was removed were not different from normals in the object learning or object reversal. All the lesion groups including the hippocampal were impaired on the place reversal. The occurrence of deficits on spatial tasks of this kind is characteristic of hippocampal lesions and will be discussed later. However, the measure of stimulus reinforcement association that is represented by the object reversal was not disrupted by hippocampal lesions, but was disrupted by anterior temporal and orbital frontal lesions.

There are a number of experimenters who have noted a similarity between the effects of human medial temporal lesions and temporal cortex lesions in monkeys (Chow and Survis, 1958; Iversen and Weiskrantz, 1964; Dean and Weiskrantz, 1974). In order to explain this similarity, Iversen and Weiskrantz postulated that there was a movement of temporal cortex in evolution so that monkey inferotemporal cortex becomes ventral and medial in the human brain and was therefore removed with Scoville's medial temporal lobectomies.

Destruction of the amygdala produces such a profound drop in emotionality that it has often been credited with being responsible for the Klüver-Bucy syndrome. The learning deficits, however, do not occur with removal of the amygdala (Pribram and Bagshaw, 1953; Mishkin, 1954; Schwartzbaum, 1965; Horel *et al.*, 1975) and the emotionality changes (as well as the visual discrimination deficit) can be produced if care is taken to remove all of the anterior temporal neocortex, leaving medial structures, including the amygdala, intact (Akert, Gruesen, Woolsey and Meyer, 1961; Horel *et al.*, 1975).

Hippocampal lesions produce deficits on spatial problems and some of these results will be discussed later, but the majority of experimenters have failed to find general impairments of learning and retention with hippocampal lesions. No deficits are seen on visual discriminations (Mishkin, 1954) object reversals (Mahut, 1971; Jones and Mishkin, 1972), matching to sample (Correll and Scoville, 1965*b*; Mishkin and Oubre, 1976), delayed response (Orbach, Milner and Rasmussen, 1960; Mahut and Cordeau, 1963; Mahut, 1971) and a wide variety of other learning tasks in various species (*see* reviews by Douglas, 1967; Kimble, 1968; Isaacson, 1972; Jarrard, 1973).

Thus in dissecting the Klüver-Bucy syndrome with lesions in monkeys, it seems that emotionality changes are produced either by damage to the amygdala or neocortex while learning and perceptual defects are produced by the cortical lesions but not by hippocampal lesions.

Memory in animal experiments. It is currently the fashion to regard tasks used in animal research such as the two-choice visual discrimination as unrepresentative of the kinds of learning and memory displayed by humans. In a recent review of the evidence for this suggestion, Iversen (1976) starts with the assumption that the memory defect in humans is due to hippocampal damage. She rejects the suggestion that the lack of correspondence with animal observations is due to the uniqueness of the human brain. This forces her to conclude that the problem must lie with the tasks that are used with animals: 'It is thought that simple associative learning of this kind puts very little pressure on the kind of dynamic information-handling process envisaged to transfer input from temporary to permanent storage'. She suggests delayed alternation and delayed response come '... closest to the kind of task that in humans requires dynamic interaction between short- and long-term memory; this type of task is impaired by hippocampal damage (Mahut, 1971), fornix section (Mahut, 1972) and anterior cingulate lesion (Pribram *et al.*, 1962)'. Iversen concludes that involvement of delayed alternation or delayed response are the only hope for evidence of monkey memory defects with hippocampal lesions.

However, as we shall see, delayed response and delayed alternation experiments provide no support for the hippocampal memory hypothesis. In the delayed response task, one of two foodwells is baited in full view of the monkey and then both wells are covered. After a delay, the foodwells are placed within the animal's reach and it must remember which one was baited. The same two foodwells are used in the delayed alternation task, but here they are baited out of the view of the animal. On one trial the left well is baited and on the next the right is baited and so on. A delay is imposed by the interval between trials and the animal must remember which side was rewarded on the last trial to perform correctly.

It is interesting that in an early study on the effects of hippocampal lesions on delayed response and delayed alternation, Orbach, Milner and Rasmussen (1960) noted that 'An analysis of the human temporal lobe data led us to predict that no disturbance in performance of the standard delayed response would be seen (nor for that matter in performance of delayed alternation, a prediction which proved correct in the one instance but not the other)'. They felt that distractions would have to be inserted into the delay period to produce deficits like those seen in human amnestics. In this study, as in others (Mishkin, 1954; Mahut and Cordeau, 1963; Mahut, 1971) no deficit is seen on delayed response, with or without distractions, if the lesion in the monkey is restricted to the hippocampus.

It is also unlikely that the delayed alternation deficit which is seen after hippocampal lesions is a defect in 'the kind of task that in humans requires dynamic interactions between short- and long-term memory'. Delayed alternation is a spatial task in which the animal must go left on one trial, right on the next, left on the next and so on, with a delay between one trial and the next. If the task is made nonspatial by using a go no-go paradigm (respond on trial one, not on trial two, respond on trial three, etc.) where the animal responds to a single place, hippocampal animals show no deficit. Another way to make the task nonspatial is to use the object reversal task which was already described. On trial one, response to object A is rewarded, on trial two object B is rewarded, on three, A is again rewarded, etc. The side that A and B are on is irrelevant to solving the task. Hippocampal lesions produce no deficit on this nonspatial object alternation task either (Mahut, 1971).

Thus, if the spatial aspect of the delayed alternation task is eliminated, hippocampal animals have no deficit. Probably the major thrust of current hippocampal research is on its spatial functions. Lesions of hippocampus, fornix or mamillary body produce deficits on tasks that require determining one's position in space; and hippocampal cells discharge in relation to spatial position cues (O'Keefe and Dostrovsky, 1971; Mahut, 1972; O'Keefe, Nadel, Keightly and Kill, 1975; Rosenstock, Field and Greene, 1977; Jarrard, 1978; Olton, Walker and Gage, 1978). We have already noted the deficit observed by Jones and Mishkin (1972) that animals with hippocampal lesions display on a spatial reversal task, but not on object reversals. Thus it is the spatial nature of these tasks, not their mnemonic feature, that disrupts the performance of animals with hippocampal lesions.

Electrical correlates of hippocampal memory. Although the animal experiments are overwhelmingly negative on the effects of lesions to the hippocampus on learning and memory, a number of laboratories have found electrical correlates of learning in the hippocampus (*see* Adey, Kado, Didio and Schindler, 1963; John and Killam, 1960; Olds, 1970). A recent example is the observations of Thompson and his colleagues (Thompson, 1976; Berger, Alger and Thompson, 1976). This work is a continuation of Lashley's search for engrams and carries the search to the hippocampus because of the Scoville and Milner observations. These workers studied the activity of single cells in the hippocampus during the conditioning of the nictitating membrane of the rabbit. They found cells whose activity correlated very highly with the conditioning process (pairing of CS and UCS produced an increase in the response of the units to the CS). They concluded that this indicates the presence of engrams, or memory traces in the hippocampus.

However, Schmaltz and Theios (1972) and Solomon and Moore (1975), using the same animal and task, found no deficit in the acquisition and retention of the conditioned response with hippocampal destruction. In fact the CR was acquired more rapidly without the hippocampus. Thus, although information on conditioning is available to the hippocampus, an intact hippocampus is not necessary for it.

Electrophysiological correlates of learning and recall processes occur throughout the brain in areas where lesions are without effect in learning or memory (John, 1972). Thus physiological recording is of little help in defining the anatomical structures responsible for the severe amnestic disorders that are known to occur with limited brain damage.

It is apparent that the evidence for the conclusion that hippocampal lesions produce memory impairments rests entirely upon observations on humans. Efforts to bend the animal data to fit such a conclusion have been unsuccessful.

The Human Temporal Lobes and Memory

Amnesia from posterior cerebral artery disease. Except for one of Penfield and Milner's patients, which will be discussed later, the most celebrated cases of temporal lobe amnesia have not been brought to autopsy and we must rely in these cases on the judgement of the surgeons as to the structures removed. There are a few cases of memory disorders, however, that result from posterior cerebral artery occlusion on which histology has been done and these cases have been used to support the hippocampal memory hypothesis (Glees and Griffith, 1952; Van Buren and Borke, 1972; Victor, Angevine, Mancall and Fisher, 1961). All these patients obtained their bilateral medial temporal lesions from diseased posterior cerebral arteries.

The posterior cerebral artery supplies the medial quadrant of the temporal lobe, including the hippocampus, hippocampal gyrus and at least half of the inferior temporal gyrus and the white matter underlying the cortex; the maximum extent of the distribution of this artery over the temporal lobe varies from a minimum in some specimens of half the inferior temporal gyrus, and a maximum in others which includes up to the lateral surface of the superior temporal gyrus (Beevor, 1909). The hippocampus receives much of its supply from this artery, which is a branch of the basilar artery, but some of its supply comes from the anterior choroidal artery which branches from the internal carotid (Beevor, 1909; Goldberg, 1974).

In addition, the posterior cerebral artery supplies part of the fornix, mammillary bodies, wide areas of dorsal thalamus, including the pulvinar and the anterior nuclei, the midbrain and the medial aspect of the occipital lobe.

As we should anticipate, much more than the hippocampus is involved in cases of posterior cerebral artery occlusion. Although the area injured does not include the entire distribution of the posterior cerebral artery, the pathology is extensive. Of particular interest here is that all three cases of Van Buren and Borke had severe degeneration of occipitotemporal white matter. Cutting these fibres in monkeys produces the Klüver-Bucy syndrome and an inability to relearn a pre-operatively learned discrimination (Horel and Misantone, 1974). Degeneration can be seen in the white matter of the temporal lobe in the photographs in the case of Victor *et al.* as well, and Glees and Griffith noted a decrease in the white matter of the temporal lobe in their case.

Also, as we might expect from the contribution of the anterior choroidal artery, there was considerable sparing of hippocampus in these patients. This is particularly interesting because from the surgeon's description it was probably not completely destroyed in medial temporal lobectomies either, and a failure to completely remove the hippocampus in animals is sometimes advanced as the reason for their failure to produce learning defects.

The anatomical basis of the amnesia that results from posterior cerebral artery occlusion is difficult to interpret. It confirms the results of animal and human surgery in suggesting that damage to the medial quadrant of the temporal lobe can produce deficits in learning and retention; however, it does not convincingly narrow the source of the symptoms to any particular structure within the quadrant. A similarly inconclusive source of evidence for temporal lobe memory functions derives from cases of limbic encephalitis and Alzheimer's disease.

Limbic encephalitis. Memory functions have also been associated with the hippocampus in limbic encephalitis. In these cases, encephalitis occurs in association with a carcinoma, usually of the bronchus. A salient feature of the pathology in these cases has been degeneration of ventromedial temporal lobe structures, with a particularly intense involvement of the hippocampus and amygdala (Brierley, Corsellis, Hierons and Nevin, 1960; Yahr, Duvosin and Cowen, 1965; Corsellis, Goldberg and Norton, 1968). Prominent among the many symptoms these patients display is a memory defect and this has been attributed to the hippocampal lesions. The pathology is, however, too widespread and the symptoms too abundant to use these cases for localization.

Alzheimer's disease. Alzheimer's disease is a presenile dementia that begins with a memory disorder and disorientation which becomes progressively worse ending finally in a complete dementia. Morphologically the disease appears as cortical atrophy with neurofibrillary tangles and 'senile' plaques (Sourander and Sjögren, 1970). The frontal and temporal areas seem most affected (Corsellis, 1970). In a study of 85 cases, McLardy (1970) found an absence of hippocampal damage in patients with the disease. In order to explain the Scoville and Milner observations, McLardy suggested that the amnesia is produced by lateral entorhinal damage. There is some degeneration seen in the hippocampus of patients with Alzheimer's disease (Corsellis, 1970); but, there is also severe damage to the temporal neocortex and amygdala (Sourander and Sjögren, 1970). It is interesting that the latter study reports that 80–90 per cent of Alzheimer patients have the Klüver-Bucy syndrome; nonrecognition of faces, orality, and hypermetamorphosis, symptoms which in monkeys are related to damage to temporal neocortex and amygdala (Akert *et al.*, 1961; Horel *et al.*, 1975).

Neither the lesions nor the symptoms are sufficiently limited in cases of limbic encephalitis and Alzheimer's disease to be informative about localization of symptoms of memory disorder. Somewhat more informative, although still controversial and inconclusive, are the findings on electrical stimulation of the temporal cortex.

Memory elicited by stimulation of the temporal lobe. Electrical stimulation of the exposed temporal cortex in conscious patients sometimes elicits a remarkable response in which specific memories or voices or images are produced by the electric current. It is reported that these memories are replayed during the stimulation in tape-recorder fashion (Penfield and Jasper, 1954). 'It was as though the stream of consciousness were flowing again as it did once in the past' (Penfield and Roberts, 1959). These experiential responses have only been observed in patients with temporal lobe epilepsy. Bickford et al. (1958) found that if the stimulation was in the white matter rather than in the cortex an amnesia was produced. Their electrodes were within the middle temporal gyrus.

Penfield and Jasper (1954) interpreted these observations as indicating memory storage functions for the lateral surface of the temporal cortex. However, because of the findings on medial temporal removal, these observations were re-interpreted. Penfield and Roberts (1959) pointed out that electrical stimulation creates a disturbed zone and a positive organized response identifies the function with which the stimulated area has normal connections. Thus the memory responses derived from stimulating the cortex were assumed to result from conduction to the hippocampus.

Temporal cortex, however, projects only indirectly to the hippocampus via entorhinal and perirhinal cortex medial to the rhinal sulcus in the region of the uncus (Van Hoesen and Pandya, 1975*a*). The 'prorhinal' area on the medial bank of the rhinal sulcus and entorhinal area 28 project into the subiculum which projects into the hippocampus (Van Hoesen and Pandya, 1975*b*). The temporal cortex has much more direct and robust connections to thalamus, basal ganglia, amygdala and other cortical areas, including other temporal cortex (Whitlock and Nauta, 1956). It seems likely that this entorhinal link to the hippocampus was seriously injured, if not totally destroyed, in the uncal removals that Scoville and Milner found did not produce amnesia. Learning and memory defects are not produced in monkeys with lesions in the region of the entorhinal cortex either (Mishkin, 1954; Mahut, 1972; Horel *et al.*, 1975).

The effects of stimulating the hippocampus are less clear. Jasper and Rasmussen (1958) stimulated the amygdala and hippocampus in 80 patients operated on at the Montreal Neurological Institute. In some cases they were able to directly stimulate the exposed structures. The most common response to stimulation of the amygdala were feelings or sensations relating to the alimentary tract or to a part of the body or the body as a whole. Nearly as frequently as these were some form of '. . . impairment in thinking, consciousness, or memory . . .' with amygdaloid stimulation. Hippocampal stimulation in 9 patients produced nothing to indicate memory functions for this structure. All responses seemed to be referred to vague feelings or sensations in the body or stomach.

The results of Chapman, Walter, Markham, Rand and Crandall (1967) were quite different. Bilateral stimulation of the hippocampus resulted in clouding of memory or amnesia in 2 patients. In 7 of 15 epileptic patients reports of '. . . visual images, sounds, or memory fragments . . .' were noted when the hippocampus was stimulated. Adams and Rutkin (1970) noted that human hippocampal stimulation produced images and hallucinations. They found that '. . . no two stimulations of the same anatomical point produced the same hallucinations, that certain images and hallucinations were not derived from memories of real experiences, and at times, recent perceptions, ideas or motives were present in the content of these visual events'.

Rasmussen made an important observation on stimulating the amygdala and hippocampus in the Discussion following the paper by Chapman *et al.* (1967). 'We have stimulated these regions through depth electrodes at operation in well over 300 patients undergoing operation for temporal lobe epilepsy. Almost without exception, when stimulation of the amygdala or hippocampus has produced a complex hallucinatory or interpretive response, there has been significant alterations of the electrical activity of the surface of the temporal lobe, with the normal brain waves being replaced by irregular high-amplitude slow waves, by an organized after-discharge, or by a diffuse flattening of the record. In the vast majority of the stimulations, in which the after-discharges spread from the amygdaloid region to the hippocampus, or *vice versa*, without alteration of the electrical activity of the convexity, there was either no clinical response to the stimulation, or the response consisted of a vague somatic or visceral sensory response'.

A number of animal experiments have shown a retroactive amnesia to a behaviour learned just prior to stimulation of amygdala (*see* Kesner and Doty, 1968; Gold, Macri and McGaugh, 1973) or hippocampus (*see* Kesner and Doty, 1968; McDonough and Kesner, 1971; Zornetzar, Boast and Humrick, 1974). Occasionally, facilitation of learning is seen when the hippocampus is stimulated electrically in animals (*see* Destrade, Soumireu-Mourat and Cardo, 1973). Chow (1961) produced an after-discharge in the temporal cortex or hippocampus of monkey by electrical stimulation. Bilateral temporal cortex after-discharge severely disrupted the acquisition or retention of visual discrimination. Bilateral or unilateral hippocampal discharges were without effect on retention of this task.

Of particular interest to the suggestions of this paper are the observations of Doty and Overman (1977). They trained monkeys to press a lever for a fruitjuice reward in response to a stimulus. In some cases this conditioned stimulus was an electrical stimulation of area 17; in others it was a sound (clicks) or a visual stimulus (red light). Electrical stimulation of the anterior commissure or its radiations into the temporal lobe during training completely prevented acquisition of the task. The anterior commissure is the interhemispheric connection between the two temporal lobes, interconnecting cortex, and amygdala, but not hippocampus (Zeki, 1973). Some noncommissural projections of the temporal cortex are within what is generally called the anterior commissure (Whitlock and Nauta, 1956) and at the temporal stem the anterior commissure, ansa peduncularis and other fibres of the temporal cortex run together (Whitlock and Nauta, 1956; Klingler and Gloor, 1960). It is this white matter which, when cut by Horel and Misantone, completely disrupted the ability of monkeys to relearn a visual discrimination.

The results of electrical stimulation of temporal lobe structures provide us with a somewhat confusing picture. They seem to indicate some memory function for the temporal cortex, amygdala and hippocampus. However, the most powerful and consistent effects seems to derive from stimulation of the neocortex or its medullary core. Yet, there has been a reluctance to consider memory functions for the human temporal cortex, not only because of the Scoville and Milner report, but also because of the ambiguous results of lesions of the human temporal cortex.

Lesions of human temporal cortex. In monkeys, removal of the entire temporal neocortex produces severe behavioural disorders including defective learning and retention and the entire Klüver–Bucy syndrome (Akert *et al.*, 1961; Meyer, 1958; Horel *et al.*, 1976). If the lesions are smaller the symptoms are much less and depend upon where they are placed and the task that is required (Mishkin, 1966; Gross, 1972). Damage to the white matter produces a deafferentation of cortical areas and small lesions at bottlenecks such as the temporal stem can produce devastating results. This should be kept in mind when evaluating the effects of lesions of temporal cortex in humans.

In the past it has been felt that unilateral damage to the temporal lobe in humans does not produce any deficits unless it is accompanied by contralateral pathology. However, Milner (1971, 1972) has found that if the tests are sufficiently sensitive, deficits in verbal memory can be detected with left temporal lesions and deficits in nonverbal perceptual functions are produced with right temporal lesions. Milner (1971, 1972) reported work done by Corsi in her laboratory on patients who, according to the surgeon's description of his intentions, removed just the temporal cortex, or removed the cortex plus hippocampus. Temporal cortex lesions produced impairments, but if the hippocampus was included in the lesion, the deficit was more severe. This evidence is used to support the hippocampal memory hypothesis. It is hazardous to guess at the true placement and extent of the lesions in these patients, but it seems probable that temporal cortex white matter was transected in approaching the hippocampus. This could increase the effective cortical lesion and exacerbate the memory disorder in these patients. In any case, these unilateral lesions produced deficits that are not nearly as severe as bilateral lesions.

Gol and Faibish (1967) removed the hippocampus surgically in several patients in an attempt to relieve pain. In some cases they approached the hippocampus by inserting a blade between the superior and middle temporal gyri; in other patients the lesions were performed stereotaxically. From autopsies of this material the authors felt that the memory defect correlated better with damage to temporal neocortex than to hippocampus, but they admitted that they were unable to clearly separate the effects of damage to the two structures.

Reports of large bilateral lesions restricted to the temporal cortex in humans are rare. One that appears to fit this category, although there is no supporting pathology, was reported by Petit-Dutaillis, Christophe, Pertuiset, Dreyfus-Brisac and Blanc (1954). They removed the temporal cortex bilaterally to relieve epilepsy. The removal was intended to spare the uncus and hippocampus and extended 6·5 cm posteriorly on the right and 7 cm on the left with sparing of some of the superior temporal gyrus on that side to protect language function. A month after the operation there was a retrograde amnesia for the months immediately preceding the operation but a sparing of older memories. Also, there was a 'dysmnésie de fixation (amnésie d'intégration)'. It was found that the patient could not retain the sense of a phrase which he obtained from reading. There were other psychological disorders (homosexuality, paranoia) but these were present in some form pre-operatively. Eventually the patient recovered to the point when his memory seemed satisfactory. This led the author to suggest that the temporal cortex is not involved in memory functions.

Sabourand, Gagnepain, Chatel and Menault (1976) presented a case with lesions of the temporal cortex which they felt indicated a lack of memory functions for this structure. In this case the pathology was available. The lesion resulted from a motor cycle accident which produced bilateral damage to the superior, middle and inferior temporal gyri.

The left temporal lobe lesion was massive. The hippocampus, hippocampal gyrus and uncus were spared, as was most of the superior temporal gyrus. The middle and inferior temporal gyri were almost completely destroyed. The cortical lesion extended posteriorly to the supramarginal gyrus. There was an area of necrotic white matter which extended from the middle and inferior temporal gyri into a localized area of the occipital lobe above the posterior horn of the lateral ventricle. Secondary degeneration of the white matter was scattered throughout the superior temporal gyrus and fusiform gyrus and extended posteriorly into the occipital lobe. The right temporal lobe lesion was much more circumscribed. Anteriorly the crowns of the superior, middle and inferior temporal gyri were destroyed but there was some sparing of the depths and banks of their sulci. The damage extended posteriorly to the level of the lateral geniculate nuclei where they were reduced to two shallow lesions, one on the superior temporal gyrus and another on the inferior temporal gyrus. There was some secondary degeneration in the white matter of these gyri, but the remainder of this lobe, including all of the medial structures, were intact. Retrograde degeneration occurred in the lateral half of the left lateral geniculate nucleus corresponding to the fibres of Meyer's loop. There was some pulvinar degeneration.

The patient was 15 years old at the time of the accident and was observed closely for five years before he died. During this time, he could utter no comprehensible language; his spontaneous sounds were inarticulate and uninterpretable. He was unable to follow commands and would 'echo' commands if given orally or imitate the gestures if the commands were demonstrated. He was unable to identify objects or pictures placed before him nor place labels on pictures. Extensive attempts to re-educate him met with little success. The reason for claiming that his memory was intact was that in attempting to train him they had him copy pictures. When presented with a model to copy which he had already done, instead of slavishly copying it, he would search for it in the pages of his copy book or look for it in a drawer. It is interesting in the light of the perceptual properties discovered for the right temporal lobe (Milner, 1971, 1972) that the right temporal cortex was the least injured and picture copying was performed effectively by the patient and he had evidence of memory for these pictures. Also, he was able to differentiate between family and non-family, friends and disciplinarians, nurses and physicians. But, within those classes his reactions were identical—without distinctions that would permit one to suppose that he knew the differences of the roles and positions of these people. The intellectual status of this patient was very much like that of the case of bilateral temporal lobectomy described by Terzian and Orre discussed earlier. However, in this case the hippocampus and amygdala were intact.

These observations are not inconsistent with the results of lesions of the temporal cortex in animals. In the second case there was one small indication of intact memory processes in an otherwise incredibly devastated cognitive functioning that did not recover. Animals with complete temporal cortex removal can learn (Meyer, 1958) and H. M. with his medial temporal lesion can learn some tasks as well (Milner *et al.*, 1968). Thus temporal lesions of any kind do not produce a total inability to learn, but for reasons that have not been decided they do produce very severe learning disorders. Recovery of function is also frequently seen, especially with smaller lesions. It is not clear, in the first case above, how much tissue was actually removed or whether the patient returned completely to normal in his cognitive functions. It is clear that he did have a very severe memory disorder that lasted several months. I would like to suggest that if the damage to the temporal cortex is large enough, a more profound and permanent defect would be seen, as in the case reported by Sabourand *et al.* (1976), and as is seen with lesions of the temporal cortex in animals. H. M. is not nearly as severely affected as the case reported by Sabourand *et al.*, except for picture recognition in the Sabourand case which is explained by intact temporal cortex on the right side. H. M. retains his pre-operatively learned skills and his ability to differentiate between people he knew pre-operatively, but with a few exceptions he cannot learn new skills or differentiations. The case reported by Sabourand *et al.* seems to have lost his pre-traumatic skills and differentiations as well as his ability (again with a few exceptions) to acquire new tasks. However, H. M.'s disability can be considered to be contained within the larger deficit presented by the Sabourand case.

Thus, an even more severe amnesia can be produced with large temporal cortex lesions than with medial temporal removal. I believe that the two effects are related in that the medial temporal lesions are cutting some of the fibre tracts of the temporal cortex.

Temporal Stem Lesions and Memory

Injury to the temporal stem in humans. Scoville (Scoville, Dunsmore, Liberson, Henry and Pepe, 1951; Scoville and Milner, 1957) approached the medial temporal lobes through a supraorbital trephination. The tip and medial surface of the temporal lobes were exposed and the temporal tips were bisected. The resections were then extended posteriorly with a suction tip and a spatula, dissecting out the uncus, amygdala, anterior hippocampus and hippocampal gyrus.

The question raised here is whether or not such a lesion could damage the temporal stem and whether or not such damage could produce defects of learning and memory. An examination of the white matter of the human temporal lobe reveals that some of it crosses directly in front of the hippocampus (Klingler and Gloor, 1960; DeArmond, Fusco and Dewey, 1976, fig. 82). These fibres are necessarily transected by the medial temporal lobe excisions. From the description of Klingler and Gloor (1960) of the projections of this white matter, it would appear to be impossible to make these lesions without transecting at least the ansa peduncularis, as well as other temporal lobe pathways.

In addition to these fibres that had to have been transected, it seems likely that other parts of the temporal white matter were injured by these lesions. As we move posteriorly to the hippocampal region, the temporal stem is seen as a band of white matter directly across the narrow slip of the inferior horn of the lateral ventricle (fig. 1). The further posteriorly these lesions extend as the tissue is retracted to expose the hippocampus, the more likely that this fragile white matter will be damaged. In addition, the blood supply to the ventromedial quadrant of the temporal lobe, including the white matter, is by way of branches from the posterior cerebral artery that penetrates through the tissue that is removed by the operation (Beevor, 1909). The same surgeon, using the same method of removing the medial temporal lobe, consistently damaged the temporal stem of monkeys (Correll and Scoville, 1965*a*, *b*). Later, we will examine these data to determine if the stem lesions had an effect on performance.

Penfield and Mathieson (1974) have presented the autopsy findings on Case B of Penfield and Milner (1958). In this patient a severe and permanent amnesia followed removal of one temporal lobe. The temporal lobe was removed in two stages separated by several years. In the first operation, the uncus and hippocampus were spared and there was no amnesia. The second operation was performed because of an increase in epileptic attacks. At this time the anterior half of the hippocampus and the uncus were exposed and removed. The result was the well-known anterograde and retrograde amnesia characteristic of medial temporal injury. The authors speculated that the patient had a defective hippocampus contralateral to the injury so that the operation removed the only remaining functional hippocampus.

Autopsy revealed that the hippocampus contralateral to the temporal lobectomy was shrunken and its associated fornix was reduced in size, which is consistent with Penfield and Milner's predictions. However, on the lesion side, the posterior 22 mm of the hippocampus was intact and appeared normal except for a thinning of the alveus which was probably secondary to the removal of the anterior end of this structure. Gliosis was seen in the white matter in the intact part of the temporal lobe on the side of the lesion and in the contralateral temporal lobe as well.

In the photographs of the fibre-stained material, this degeneration is clearly apparent as a pale area in the darkly stained temporal white matter. The temporal stem appears to be completely degenerated in these pictures. In fact a comparison of the photographs of the hippocampus and temporal lobe white matter (Penfield and Mathieson's figs. 5–8) suggest that the temporal stem was more severely damaged than the hippocampus. Exposure of the hippocampus must have damaged the temporal stem in that part of the temporal lobe not removed in the original lesion just as I suggested must have occurred in Scoville's surgery. The autopsy reveals degeneration of the contralateral stem and some degeneration of the temporal medulla as well. I propose that it is this bilateral damage to the temporal stem and white matter of the temporal medulla that is responsible for the amnesia of these patients, not the partial hippocampal damage.

The temporal stem or albal stalk contains fibres that interrelate temporal cortex and amygdala with other brain structures (Klingler and Gloor, 1960; Nauta, 1961, 1962; Whitlock and Nauta, 1956; Zeki, 1973). The corticocortical connections that enter the white matter of the temporal lobe posteriorly are uninjured by the temporal stem lesions which we are discussing here. The projections to the posterior thalamus and midbrain (Whitlock and Nauta, 1956) must be spared by the anteriorly placed temporal stem lesions.

However, there are a number of important connections in the lesion area. Within this area are the uncinate fasciculus which interconnects the orbital surface of the frontal lobe and the temporal lobe, temporal cortex projections to the medial magnocellular part of the medialis dorsalis (DMm), the ventral part of the putamen, the claustrum, the tail of the caudate, thalamic reticular nucleus and zona incerta (Whitlock and Nauta, 1956; Reitz and Pribram, 1969). The intertemporal component of the anterior commissure forms a large part of the temporal stem; some of the fibres that are within this massive tract labelled anterior commissure do not decussate, however, but terminate in the medial thalamus (Whitlock and Nauta, 1956). Fibres to DMm run in the ansa peduncularis and some run for a time in the temporal limb of the anterior commissure. The ansa peduncularis is a large fibre tract containing many diverse elements that extends through the sublenticular gray matter. It should not be confused with the nearby unrelated ansa lenticularis. The ansa peduncularis has been described by Nauta and Mehler (1966) and Klingler and Gloor (1960) and is illustrated in fig. 59 in the DeArmond *et al.* (1976) Atlas. Some of the temporal projections exit from the ansa peduncularis and join the inferior (or extracapsular) thalamic peduncle which enters the DMm (Whitlock and Nauta, 1956; Klingler and Gloor, 1960). There are also amygdaloid efferents in the temporal stem (Nauta, 1961) and projections back to the amygdala from DMm (Nauta, 1962). It is interesting that although there are projections to DMm from the temporal cortex, no reciprocal connections were noted (Nauta, 1962). However, DMm projects to orbital cortex (Akert, 1964; Nauta, 1964) and orbital cortex projects to temporal cortex via the uncinate fasciculus.

From this description it is apparent that the narrow band of white matter that forms a bridge between the medullary core of the temporal lobe and the capsules of the brain-stem represents a bottleneck through which flows a diversity of major pathways. What are the consequences of obstructing this crossroad which is so crowded with temporal lobe information?

Injury to the temporal stem in monkeys. We transected the temporal stem in two ways: one by an approach through the lateral sulcus and one through an anterior approach in the same manner as Scoville's removal of the medial temporal area (Horel and Misantone, 1974, 1976). Post-operatively, animals with their temporal stem transected performed at chance for 1200 trials on a visual discrimination task they had easily learned pre-operatively in 250–600 trials. Normal animals show excellent retention of such tasks over the same period of time. Some of the Klüver–Bucy syndrome, such as a drop in emotionality, was present as well, but amygdala damage complicates the interpretation of that effect. These emotionality changes can be produced by destruction of the amygdala without disrupting retention of this task (Horel *et al.*, 1975). The animals seemed otherwise normal and worked readily on the task.

In searching the literature we discovered a number of studies in which the temporal stem had been inadvertently damaged while attempting to destroy nearby structures. Divac, Rosvold and Szwarcbart (1967) destroyed the tail of the caudate nucleus and found deficits in visual discrimination performance. From the limited histology they present, it appears that the lesions also invade the temporal stem, particularly the ansa peduncularis and temporal limb of the anterior commissure. They looked for these deficits with lesions of the tail of the caudate because of the projection it receives from the temporal cortex.

Buerger, Gross and Rocha-Miranda (1974) also attempted to block the output of the temporal cortex, but with ventral putamen lesions. Operated animals were significantly impaired on the retention of a visual pattern discrimination. Rank order correlation between amount of damage to the part of the putamen which receives the greatest amount of temporal cortex projections and performance deficit was 0·50 ($P < 0{\cdot}05$). The correlation between the severity of the impairment and damage to the temporal stem ('external white matter') was 0·73 ($P < 0{\cdot}01$). It is interesting that damage to the temporal stem anterior or posterior to this putamen area which receives a heavy temporal cortex projection did not correlate with severity of deficit ($r_s = 0{\cdot}12$). This suggests that there may be a limited part of the stem that is critical for the performance of these tasks.

Of even more direct relevance for the theme advanced here are the findings of Correll and Scoville (1965*b*). By the mid 1960s it had become apparent that the usual learning and retention tasks that were used with animals were unaffected by lesions which were confined to the hippocampus. This prompted Correll and Scoville to turn their attention to the '. . . structural aspects of the problem' and attempt to 'replicate more closely certain parameters of a human memory task'. For this they chose a delayed matching to sample task. The animal is first presented with a sample stimulus. After a delay it is presented with two simuli, one of which matches the sample. If it responds to the stimulus that matches the sample it is rewarded and if it does so consistently this is evidence that it remembered the sample over the delay interval.

In one group the tissue that was removed and the surgical approach used was exactly like that of the large medial temporal lobectomies in humans in which the uncus, amygdala and hippocampus were removed; in another group the same approach was used, but only the amygdala and uncus were removed. In a third group the hippocampus and hippocampal gyrus was removed by a suboccipital approach instead of the anterior approach that was used in the other animals. Finally, there was a group of sham operates. Fortunately, the authors provide a detailed table of the damage that was done to each animal and each animal's score on the task. A severe deficit is seen in performance on the match and delayed match condition in the medial temporal group. The animals with amygdala lesions performed worse than controls, but not significantly so. But the group in which the hippocampus was removed by an occipital approach showed no evidence of a deficit on this task.

The authors believed that damage to the temporal stem was not responsible for the effects that they observed because animal A57 had a deficit without evidence of stem damage. However, examination of their Tables suggests that A57 is the exception rather than the rule. The animals with medial temporal lesions had severe damage to the temporal stem and had severe deficits on the task. The animals in the amygdala group had slight damage to the temporal stem and slight deficits on the task, while the animals in which the hippocampus was removed by a suboccipital approach had no stem damage and no deficit. I performed a rank order correlation on these data between the deficit on the match condition for all lesion groups and the amount of damage listed for the temporal stem in their Table. The correlation was 0·80 ($P < 0{\cdot}01$). Inspection of their Tables 1 and 4 suggest that a correlation between the deficit and stem damage is not limited to the match condition but is present in the delayed matches as well. Therefore, if the medial temporal lobectomy is performed on monkeys in the same way that it was done on humans, damage to the temporal stem is produced and a deficit on delayed matching to sample is seen. But if the hippocampus is removed in such a way as to spare the stem, there is no deficit.

If the Correll and Scoville deficit in delayed match to sample is due to stem damage, the deficit should also be produced by temporal cortex damage, and this has been found (Dean, 1974; Mishkin and Oubre, 1976). Dean extensively overtrained his monkeys on delayed match before making lesions in the inferotemporal cortex. Post-operatively they showed no retention of the task—a 'retrograde amnesia'. They were also initially unable to relearn the task even at zero delay which could be interpreted as prograde amnesia. After extensive retraining on simpler problems and thousands of trials, Dean finally got two of his animals to reach criterion at zero delay. Once they reached criterion they performed normally at all delays up to thirty seconds. This capacity to remember stimuli over short intervals is remarkably like the 'immediate memory' that is undisturbed in human amnestics. Thus, Dean's monkeys like H. M. have a retrograde and prograde amnesia with an intact immediate memory. It seems likely that if Correll and Scoville had pushed the training of their monkeys as far as Dean, they too would have reached the point where they could perform normally at the same delays, thus exhibiting an intact 'immediate memory'.

Dean's monkeys had great difficulty relearning the matching task post-operatively, but once they finally acquired it, there was no apparent decrement in performance from day to day. Monkeys with inferotemporal lesions are impaired in reaching criterion, but once a task is acquired, retention is normal (Gross and Footnick, 1966, cited by Gross, 1972). Similar observations have been made on human amnestics. Milner *et al.* (1968) demonstrated that H. M. could learn a simplified maze, although with great difficulty. When tested two years later, he showed excellent retention of the task (Milner, 1970). He was also able to retain a picture recognition task over a four-month period.

Stepien, Cordeau and Rasmussen (1960), Orbach *et al.* (1960) and Correll and Scoville (1965*a*) also made large medial temporal lesions in monkeys with the intention of duplicating the human surgery. Stepien *et al.* (1960) (histology, reported in Cordeau and Mahut, 1964) and Orbach *et al.* (1960) did not examine their histology for stem damage. Orbach *et al.* found pulvinar degeneration with their lesions which indicates that they invaded temporal white matter. They attempted to control for this by making pulvinar lesions, but if they damaged the thalamic projections of the pulvinar to the temporal cortex, they must have damaged some of the other tracts in the stem as well. Correll and Scoville (1965*a*) reported stem damage in their histology, but unlike their delayed match experiment, they do not present individual scores and they have no group with only hippocampal lesions.

Thus, we cannot determine from these three medial temporal experiments what role the temporal stem may have played in the performance of the animals. However, all the medial temporal groups in these experiments displayed deficits which are also produced by temporal cortex lesions, and some of these have not been found when the lesion is restricted to the hippocampus or amygdala. Stepien *et al.* (1960) trained their animals on compound visual or auditory stimuli. Two signals were presented separated by a short interval; if they were the same the animals responded, if they were different they withheld their response. Superior temporal lesions produced deficits when auditory stimuli were used and inferior temporal lesions produced deficits when visual stimuli were used. The medial lesions, which included injury to amygdala, hippocampus and probably stem as well, produced deficits on both the auditory and visual tasks.

Orbach *et al.* (1960) found deficits in retention of pre-operatively acquired visual discriminations, no deficit in the post-operative acquisition of a simple visual discrimination (in spite of distractions) and a severe impairment in the acquisition of a visual pattern discrimination. As discussed previously, lesions restricted to the hippocampus (*see* Mishkin, 1954) do not produce deficits in acquisition and retention of visual discriminations, nor do amygdaloid lesions (*see* Horel *et al.*, 1975); however, temporal cortex lesions (Mishkin, 1954) and temporal stem lesions (Horel and Misantone, 1974, 1976) do produce severe deficits on these kinds of tasks. It seems likely from the pulvinar degeneration in the study by Orbach *et al.* that the temporal stem was injured and that the visual discrimination deficits were due to that injury.

Orbach *et al.* also found a deficit on delayed alternation in their medial temporal animals and, as discussed earlier, deficits on this spatial task are attributable to the hippocampal damage. They found no deficit on delayed response and there are no deficits on this task with temporal cortex lesions either (*see* Harlow, David, Settlage and Meyer, 1952; Mishkin, 1954), which has been interpreted as evidence for an intact immediate memory analogous to that of amnestics. The animals of Orbach *et al.* were later retested for retention on some of the tasks that they had acquired post-operatively and for the most part, retention was very good. As mentioned above, this is characteristic of animals with temporal cortex lesions and of human amnestics.

The visual discrimination experiment of Correll and Scoville (1965*a*) presents some problems of interpretation. The animals were trained on visual pattern discriminations in which either one pair of stimuli or two pair or three pair or six pair were presented serially in one session. They found no statistically-significant impairment on the one pair problem, which is simply a two choice visual discrimination. Deficits were found on the multiple pair problems. Their failure to find severe deficits on the two choice visual discrimination in the presence of stem damage is not consistent with the findings of Horel and Misantone (1974, 1976). Correll and Scoville, however, state in their discussion that 'There is also a tendency for Ss with the most involvement of the temporal stem to show the poorest scores on the one pair problem, but not on the six pair problem.'

The medial temporal animals had severe deficits on the multiple discrimination task and this task is nearly identical to the concurrent object discrimination used by Iwai and Mishkin (1968) and Cowey and Gross (1970) as a test of associative learning. They found that anterior temporal cortex lesions severely disrupt performance of this task. More posterior inferotemporal lesions disrupt learning and retention of two choice visual discriminations while anterior lesions are much less effective in producing deficits on this task. It is probably fibres from the more posterior cortex that were injured by Buerger *et al.* (1974). They found that lesions placed more anteriorly in the stem were less effective in producing visual discrimination deficits. Therefore, it is possible that the stem lesions in the Correll and Scoville multiple discrimination experiment were concentrated anteriorly and disrupted the anterior temporal cortex system. Their temporal stem lesions must have been limited, otherwise I would predict from our results that they would never have got past their first and simplest task.

With the exception of the Correll and Scoville delayed match experiment, the medial temporal experiments provide us with no direct evidence on the involvement of the stem in the observed symptoms. However, it seems likely that it was injured in all of them. Most of the symptoms that were produced by these lesions have also been produced by temporal cortex lesions. Some of these have not been found in other experiments when the lesions were restricted to the hippocampus or amygdala. Spatial delayed alternation is an exception to this and is related to hippocampal damage. It seems to be a reasonable suggestion that the temporal-cortex-like symptoms were produced by stem injury. Stem damage was unintended in all these experiments and where it was measured, varied widely in amount and in the severity of the symptoms which were produced.

The humans with large medial temporal lesions that included the hippocampus must have suffered some stem damage. Severe bilateral stem damage is clearly evident in the one case for which there is pathological evidence. With stem damage we should expect symptoms of temporal cortex injury. The most prominent symptoms these patients display are a retrograde and prograde amnesia with an intact immediate memory. Comparable deficits have been seen in animals with temporal cortex lesions—pre-operatively learned tasks are lost and they exhibit an extreme difficulty or an inability to learn new tasks post-operatively. They perform normally on measures of immediate memory such as delayed response and delayed match to sample if the task can be learned. A similar pattern of symptoms has not been described with lesions restricted to the hippocampus or amygdala. However, if large medial temporal lesions are made in animals by operations similar to those which have been performed on humans, temporal stem injury occurs and symptoms characteristic of damage to temporal cortex are apparent. It is the argument of this paper that it is injury to the connections of the temporal cortex within the stem that is responsible for the amnesia which is seen in humans with medial temporal lobe lesions.

Structures related to the temporal stem. The temporal stem contains a number of diverse projections of the temporal cortex and amygdala. One source of evidence on the fibre tracts within the stem which are responsible for the symptoms that follow its injury is the effects of damage to their separate origins and terminations. The cortical projections to the pulvinar and midbrain are probably not responsible for the deficits that we are seeking, both because the pathways to them from the temporal lobe were probably spared with medial temporal lesions and because damage to them does not produce comparable results. Early reports of tectal damage in primates did suggest important visual deficits. However, the majority of experiments on tectal and pretectal lesions in primates report trivial effects on such tasks as visual discriminations (Anderson and Symmes, 1969; Keating, 1976). Also, pulvinar lesions do not affect tasks which are sensitive to temporal lobe damage (Chow, 1954; Mishkin, 1972; Ungerleider, Ganz and Pribram, 1977). Lesions to this structure produce deficits that are more characteristic of tectal than temporal damage (Chalupa, Coyle and Lindsley, 1976).

The temporal neocortex also projects to the tail of the caudate and to the ventral putamen and lesions in both these areas have been reported to cause visual deficits (Divac *et al.*, 1967; Buerger *et al.*, 1974). However, as mentioned, the interpretation of these results is complicated by the fact that in both these studies the lesions invaded the temporal stem.

The effects of lesions of the orbital cortex bear some resemblance to those due to damage to temporal cortex (Butter, McDonald and Snyder, 1969; Jones and

Mishkin, 1972; Passingham, 1972). These findings cause one to look with interest at medial magnocellular medialis dorsalis which receives projections from the temporal cortex through the stem and projects to the orbitofrontal cortex. Here we encounter the interesting suggestion of Victor, Adams and Collins (1971) that it is damage to medial magnocellular medialis dorsalis and not the mammillary bodies that is responsible for the memory defect of Korsakoff's psychosis. This requires careful examination, because the attribution of these memory defects to the mammillary bodies has been one of the mainstays of the hippocampal memory hypothesis.

Korsakoff's Psychosis and the Temporal Stem

Relationship of Korsakoff's psychosis to the medial thalamus. Korsakoff's psychosis results from a thiamine deficiency generally secondary to chronic alcoholism. This produces degeneration of neural tissue along the walls of the third ventricle, cerebral aqueduct and fourth ventricle. The degeneration is unevenly distributed over these structures and affects different structures in different people but generally produces bilaterally symmetrical lesions (Victor *et al.*, 1971). Korsakoff's psychosis occurs when the degeneration is around the third ventricle and presents as a severe learning and memory defect sometimes with confabulation which is much like that which follows medial temporal lobe lesions. Early memories remain relatively intact and there is a period of retrograde amnesia and an anterograde amnesia (Seltzer and Benson, 1974, but *see* Sanders and Warrington, 1971).

The memory defect in Korsakoff's psychosis is generally attributed to the high incidence of degeneration of the mammillary body that is seen in these patients (Malamud and Skillicorn, 1956; Barbizet, 1963). This finding obviously connects Korsakoff's memory defect to the hippocampus by way of the fornix. However, the same problem exists for the connection of mammillary bodies to memory as for the hippocampus and memory hypothesis: learning and memory defects have not been found with mammillary lesions in animals (Ploog and MacLean, 1963; Dahl, Ingram and Knott, 1962; Woody and Ervin, 1966; Kim, Chang and Chu, 1967). Mammillary lesions, like hippocampal lesions, produce deficits on spatial tasks (Rosenstock, Field and Greene, 1977).

Victor *et al.* (1971) studied 245 patients with Wernicke-Korsakoff's syndrome, 82 of them brought to autopsy. They found the memory disorder to be associated with degeneration of magnocellular medialis dorsalis but not consistently with mammillary disease. Five patients had severe degeneration of the mammillary bodies but no learning or memory defect.

The disease first damages the ventromedial part of the magnocellular medialis dorsalis. This is the point of entrance for the temporal projections to this structure that come from the temporal stem and ansa peduncularis (Klingler and Gloor, 1960). As the disease progresses it penetrates deeper into the brain structures, damaging first and most severely the magnocellular medialis dorsalis.

Amnesia from medial thalamic lesions in humans. The dorsomedial nucleus is a large structure on the medial aspect of the dorsal thalamus. It is divisible into three distinct subnuclei each having different anatomical relations with the frontal lobe (Pribram, Chow and Semmes, 1953; Nauta, 1964; Akert, 1964; Leonard, 1972; Tanaka, 1976). The pars multiformis and the pars paralaminaris relate to the dorsal surface of the frontal lobe. The magnocellularis is the most medially situated of the three and projects to the orbital and medial frontal cortex. We have already noted the projection from temporal cortex to magnocellularis. The magnocellularis also receives projections from the amygdala (Nauta, 1962), from the septal region and the midbrain tegmentum by way of the medial forebrain bundle (Guillery, 1959). The latter regions have been associated with reinforcement functions because they are potent self-stimulation sites (Olds and Olds, 1963). Guillery (1959) noted that these anatomical relationships permit the dorsomedial nucleus to monitor both the input and output of the hypothalamus.

There is a substantial collection of clinical cases in which impairments of memory were produced by medial thalamic injury. Smythe and Stern (1938) described six cases of tumours of the thalamus. If the tumours originated in the lateral part of the thalamus, gross sensory disturbances were observed in the early stages of the illness. Tumours that originated medially were characterized by 'mental deterioration' including memory loss and early conjugate and ocular palsies. Sensory disturbances were absent or appeared late.

Stern (1939) presented a case of presenile dementia that appeared to be much like Korsakoff's psychosis including the memory defect and confabulation. This patient had bilateral thalamic degeneration.

Spiegel, Wycis, Orchinik and Freed (1955) performed dorsomedial nuclear thalamotomies in 30 cases for the relief of emotional disturbances or intractable pain. X-rays of pantopaque droplets injected at the site of the lesion confirmed that the lesions involved principally the dorsomedial nucleus. The effect on the patients was similar to that of Korsakoff's psychosis including memory defects.

Schulman (1957) reported a patient with memory deficits from thalamic damage in which the magnocellular medialis dorsalis appears to be spared. The patient had progressive dementia, including amnesia, disturbances of affect, ataxia and choreoathetosis. Much of the dorsal thalamus was degenerated in this patient including most of dorsomedial nucleus except the magnocellular medialis dorsalis which appeared as a rim of large cells medial to the otherwise destroyed nucleus. It may be that some other thalamic area is critical for the memory defect, or magnocellular medialis dorsalis or its connections could have been more severely injured than the study indicated.

Teuber, Milner and Vaughan (1968) studied a patient with a persistent anterograde amnesia that resulted from a stab wound in the brain. In this patient a fencing foil entered the right nostril, punctured the base of the brain and took an oblique upward course, slightly to the left. The course of the foil suggests the likelihood that the medial thalamus would have been injured. Paralysis of upward gaze and diminished pupillary reactions suggest that the lesion extended to the pretectum. Like H. M., this patient has a persistent anterograde amnesia. The degree of retrograde amnesia is not clear. The deficit is much worse for verbal than for nonverbal material, which is consistent with the slightly leftward course of the foil. The amnestic syndrome in this case was not accompanied by any evidence of seizures, which tends to rule out the abnormal EEG of H. M. as a necessary condition for anterograde amnesia. This patient was recently re-examined by Squire and Slater (1976). They found that memory for events prior to the injury were normal, but there was a marked deficiency for memory of events since the injury which occurred in 1960.

Recently, McEntee, Biber, Perl and Benson (1976) reported a severe amnestic case who was found to have bilateral metastatic tumours invading the medial and posterior thalamus. The mammillary bodies, mammillothalamic tract and anterior thalamic nuclei were spared while the dorsomedial nucleus was largely destroyed by the tumour as well as the centromedian nuclei, medial pulvinar, habenular nuclei and stria medullaris.

Colloid cysts of the third ventricle are frequently found to produce memory defects resembling Korsakoff's psychosis. These cysts put pressure upon the walls of the third ventricle in the region of magnocellular medialis dorsalis and removal of the cyst, which interestingly usually involves transection of the fornix, generally produces a remission of the symptoms (Cairns and Mosberg, 1951; Williams and Pennybacker, 1954).

The memory defect produced by these cysts is not due to increased intracranial pressure because reduction of this pressure does not relieve the symptoms; however, draining the cyst does. As the cyst refills, the memory symptoms recur and the symptoms are again relieved by draining. This process can be carried out repeatedly (Williams and Pennybacker, 1954).

Medial thalamic lesions in animals. Early animal experiments on the dorsomedial nucleus concentrated on its relationship to the frontal lobe. Lesions in dorsomedial nucleus had little effect on the learning of visual discriminations, delayed response or delayed alternation tasks (Chow, 1954; Peters, Rosvold and Mirsky, 1956). However, the lesions in these experiments were quite small and not directed toward the magnocellular medialis dorsalis. In one experiment the lesion involved 11 to 20 per cent of the entire dorsomedial nucleus; how much magnocellular medialis dorsalis was involved is not clear. In the other study, the lesions were also quite small, involving 0 to 70 per cent (mean 38 per cent) of dorsomedial nucleus and they were directed specifically toward the parvocellular part. The connection of magnocellularis from the thalamic peduncle would be uninjured by lesions in the lateral dorsomedial nucleus.

Schulman (1964) found deficits in a delayed response and a conditional black-white discrimination in monkeys with large lesions of the dorsomedial nucleus produced by radiation. Thompson and Myers (1971) placed small lesions in the lateral dorsomedial nucleus and found no deficits on learned visual tasks. Only one of the three animals in their pretectal group (A342) however, showed a severe deficit on these tasks and it is apparent from the histology they present that most, if not all, of the magnocellular medialis dorsalis was destroyed by the lesion.

The magnocellular medialis dorsalis receives its temporal lobe connections via the temporal stem, through the ansa peduncularis and inferior thalamic peduncle. Skinner and Lindsley (1967) used a cryogenic probe to cool the inferior thalamic peduncle in cats. This disrupted performance on a single alternation bar press where the animal presses first the right bar, then the left, then the right, etc., to get a liquid food reward. In an apparent attempt to remember the lever last pressed, the experimental animals developed the strategy of leaving the paw on the bar while drinking the reward. When the animal did not use this mnemonic, its performance was even more severely impaired with cooling of the inferior thalamic peduncle.

Warren and Akert (1960) found deficits in the learning and retention of visual tasks in cats with large lesions of the dorsomedial nucleus. Chow and Randall (1964) destroyed the midline nuclei in cats. No histology is presented, but such lesions should damage the magnocellular medialis dorsalis. The cats showed a loss of a pre-operatively-acquired visual discrimination and a deficit in re-acquiring the task. The cats also appeared to have lost their memory of how to perform the task.

There are a number of experimenters who have found deficits on a wide variety of learning tasks in rats with medial thalamic lesions, although the exact structure involved has not been identified with certainty (*see* Vanderwolf, 1969; Thompson, 1963; Olton and Isaacson, 1967; Delacour, 1971; Means *et al.*, 1974). Means *et al.* (1974) summarized their results by saying that 'Rats with DMT lesions are deficient on tasks that require them to form new associations or to utilize previously established associations.' (DMT = dorsomedial nucleus.)

Thus, there is considerable evidence from both human and animal observations that medial thalamic lesions can produce deficits in learning and memory. Although this provides an alternative to the mammillary bodies as the source of amnesia in Korsakoff's psychosis, there have been some instances of amnesia that have been reported to occur with fornix lesions. We shall consider these observations next.

Fornix Lesions and Amnesia

The severe amnesia that has been attributed to damage to the hippocampus and mammillary bodies leads directly to the prediction that destroying the fornix which connects these two structures should also produce an amnesia. In confirmation of this prediction, there are some cases of amnesia in which the fornix was damaged. Although other structures besides the fornix were also damaged in these cases, the hippocampal memory hypothesis has led to the interpretation that these amnestic symptoms were due to the fornix lesion. However, the failure to find memory deficits in many cases of fornix damage has been an awkward problem for this interpretation. The following is a discussion of these cases.

Removal of third ventricle cysts often involve sectioning the fornix. Dott (1938) and Cairns and Mosberg (1951) report patients who had no memory defects after transection of the fornix. In some cases where mental symptoms were present pre-operatively removal of the cyst, which involved transection of the fornix, relieved the symptoms (Cairns and Mosberg, 1951; Williams and Pennybacker, 1954).

Van Wagenen and Herren (1940) sectioned the corpus callosum in several patients in order to relieve epilepsy. In one of these patients the fornix was sectioned bilaterally in two places: at the columns and at the body; others received a unilateral fornicotomy. The authors demonstrated in their introductory remarks that they were alert to possible memory effects. Detailed studies were made of these patients by psychologists and psychiatrists in addition to neurological and laboratory tests. No memory defects were found in any of these patients.

Garcia-Bengochia *et al.* (1954) severed the fornix bilaterally in fourteen patients in an attempt to treat their epilepsy. They report 'So far, in none of the twelve surviving cases has there been any neurological or psychological sequela'.

Woolsey and Nelson (1975) describe a patient who was found to have a tumour that destroyed the fornix bilaterally. Microscopic examination revealed an adenocarcinoma which replaced the bodies of both fornices. Lesions in the mammillary bodies were similar to those seen in Korsakoff's psychosis. The authors state that 'He had no apparent memory disturbance as judged by an extensive detailed history that corresponded to that taken eight months earlier'. In addition 'The patient's sister, an intelligent and observant woman with whom he lived, denied that he had shown any mental abnormality prior to final hospitalization. She described their discussion of recent events and stated that she frequently instructed the patient in chores to do while she was away, and these were accurately remembered and executed'.

Nathan and Smith (1950) presented a patient who was thoroughly examined with psychological tests prior to his death from chondrosarcoma of the ilium at the age of 34 years. No behavioural or intellectual abnormalities were discovered; when he was in school he had been at the top of his class. On autopsy he was found to have an abnormal and small hippocampus bilaterally with no fornix or fimbria.

Thus, normal memory functions can be present in the absence of an intact fornix. This forces us to seek alternative explanations for the cases of amnesia which have been reported to occur as a result of fornix lesions. Otherwise we will have to accept the untidy conclusion that destruction of the fornix produces a devastating amnesia in some cases and no detectable impairment in others.

One of the cases that is used as evidence in support of the hippocampal memory hypothesis is a patient presented by Hassler and Riechert (1957) who received a bilateral fornicotomy for the treatment of epilepsy. The lesions were placed stereotaxically in the columns at the level of the anterior commissure and were produced by electrical coagulation. The first lesion was on the right side and produced no memory symptoms. Eleven months later the left fornix was coagulated and the day after this operation a severe impairment of memory appeared without evidence of other intellectual abnormality. A few days later diencephalic seizures appeared and she died eight days after the operation. At autopsy the bilateral fornicotomy was confirmed. In addition she had a tumour in the right medial frontal lobe and a softening of the left hypothalamus.

These are slender grounds upon which to build a case for memory functions for the fornix. The fornix is adjacent to the inferior thalamic peduncle in this region and the coagulation could have damaged this structure. The inferior thalamic peduncle carries fibres from the temporal cortex to the magnocellular medialis dorsalis. They course through the ansa peduncularis and this structure goes through the area of the hypothalamic softening. The anterior commissure was damaged with the second lesion. Electrical stimulation of the anterior commissure in monkeys severely disrupts performance of delayed match to sample, a memory test for monkeys (Doty and Overman, 1977). The abnormal discharges which post-operatively produced psychomotor disturbances could also have disrupted memory function.

Alternatives to the fornix can also be found for the patient reported by Sweet, Talland and Ervin (1959). This patient had his fornix cut in the process of removing a cyst from the third ventricle. Contrary to the findings of others in such cases (Dott, 1939; Cairns and Mosberg, 1951) they reported that the lesion of the fornix produced an amnesia. The pre-operative status of the memory of this patient was not reported, and that is important because such cysts often produce a memory impairment. If an amnesia was present pre-operatively it could not be due to the transection of the fornix. Usually, removing the cyst, which involves cutting the fornix, produces a remission of the symptoms (Cairns and Mosberg, 1951; Williams and Pennybacker, 1954). The surgeon could have damaged the walls of the third ventricle including the magnocellular medialis dorsalis in the process of removing the cyst.

Brion *et al.* (1969) describe a case in which the fornix was damaged bilaterally by an occlusion of the left anterior cerebral artery. The lesion was in the anterior pillars of the fornix at the anterior commissure. The left hemisphere was severely damaged and included large softenings in the course of the left recurrent artery of Heubner. There was heavy damage to the head of the caudate, the putamen and the anterior limb of the internal capsule and a sublenticular softening. There was severe degeneration of the anterior and medial thalamic nuclei probably resulting, in part, from the destruction of the internal capsule. There was also damage to the left cingulate gyrus and corpus callosum. The anterior commissure was completely destroyed.

If this lesion were bilateral the patient would be severely demented. The lesion of the internal capsule would leave him without frontal lobe function and the medial thalamic degeneration should contribute amnestic disorders. The lesions of the sublenticular and internal capsule effectively cut off the temporal connections to the medial thalamus on the side of the lesion. The temporal efferents to putamen and medial thalamus are lost on the left side.

The memory functions of the left 'speaking' hemisphere in this patient are destroyed by its various lesions and it does not have access to the memory functions of the right hemisphere because of the commissural lesions. The anterior commissure interconnects the anterior one-third of the temporal lobes (Zeki, 1973) and there is good evidence that it is significantly involved in interhemispheric communication of memories (Doty and Overman, 1977; Sullivan and Hamilton, 1973).

There are instances of amnesia produced by unilateral lesions if they are in the left hemisphere. Geschwind and Fusilo (1966) and Benson, Marsden and Meadows (1974) have presented evidence that occlusion of the left posterior cerebral artery by itself will produce an amnesia in some cases. Milner (1971, 1972) has shown that removal of the left temporal lobe will produce an impairment of verbal memory. Intellectual and memory defects with unilateral lesions in the territory of the anterior cerebral artery have been recorded previously (Critchley, 1930). Brion *et al.* (1969) point out that their patient had a deficit in spatial orientation as well as in verbal memory. The deficit in spatial orientation could be due to the bilateral fornix lesion. As discussed earlier, lesions of the hippocampus, fornix and mammillary bodies do produce deficits in spatial orientation.

Heilman and Sypert (1977) presented a patient with amnesia who had a neoplasm in the subarachnoid space of the quadrigeminal cistern. During operation it was found that the tumour had damaged the fornix bilaterally. The amnesia remained after removal of the tumour. We cannot analyse this case because there is no anatomical verification. Heilman and Sypert argue that the reason their patient had an amnesia in contrast to other cases was the position of the lesion. They speculate that fibres in the fornix destined for the thalamus would have been cut in this case but spared in the cases where the lesion was made at the columns. Cutting the fornix at the corpus callosum however, does not produce amnesia (Akelaitis, 1943; Van Wagenen and Herren, 1940). Also, this explanation would eliminate all the other cases of amnesia discussed above who had fornix lesions; they all had their lesions at the anterior pillars.

Heilman and Sypert also suggest that amnesia may be missed in many instances because of the lack of formal tests for it. However, their patient and others with Korsakoff's disease or medial temporal lesion need no special tests to be discovered. They are apparent to the most inexperienced observers, and these were not inexperienced observers.

Thus, there are clear instances of destruction of the fornix in the absence of detectable amnesia. Cases in which the fornix has been implicated in amnesia are subject to alternative interpretation. The strength of the conclusion that the fornix was responsible for the memory disorders of these patients was derived principally from the assumption that lesions of the hippocampus and mammillary bodies produce amnesia. Without that assumption there are numerous alternative explanations for the amnesia of these patients which are at least as credible.

I propose that, whatever the functions of the hippocampus, fornix and mammillary bodies, they are not the source of amnesia in brain injury. These symptoms are produced instead by a system closely associated with the temporal neocortex. This includes the temporal cortex and its white matter, the extensions of this white matter into the brain-stem and the structures to which it directly connects: basal ganglia, medial thalamus, and orbital frontal cortex.

SUMMARY AND CONCLUSIONS

The discovery that medial temporal lobe lesions produce amnesia in humans if the lesion extends sufficiently far posteriorly to include the hippocampus forms the keystone of the hippocampal memory hypothesis. Strong supporting evidence comes from the occurrence of mammillary body disease in Korsakoff's psychosis. Disease of the posterior cerebral artery confirmed the observations on the medial temporal lobectomies by showing that pathology in the ventromedial quadrant of the temporal lobe produces amnesia. The occasional piece of contradictory evidence was sufficiently ambiguous to be dismissed or re-interpreted.

Although the contradictory evidence that emerged from animal research created severe difficulties, opinion had crystallized on the matter to the degree that the data were unable to force rejection of the hippocampal memory hypothesis. This necessarily led to the conclusion that the animal model is a poor one: either the human hippocampus is unique with respect to memory or the tests which are used in animals do not tap the same mnemonic processes that are impaired by the human lesions. Both these arguments are nearly impossible to refute. The brain of every species is different and there is no way in which monkeys and humans can be tested under identical conditions.

There has never been much enthusiasm for the suggestion that the human hippocampus is so different from other animals that this uniqueness could account for the apparent differences between the behavioural effects of human and animal hippocampal lesions. However, many experimenters have devised clever tests of the possibility that the problem is in the animal behavioural measures. Given sufficient circularity of reasoning, the project must necessarily eventually be successful. The argument is that if the usual tests of learning and memory that are used with animals are not disrupted by hippocampal lesions, then these are not tests of the kinds of learning and memory defects displayed by human amnestics. One has only to search for tasks that are disrupted by hippocampal lesions in animals, and these then must tap the same memory processes that are disrupted by the human lesions.

The possibility has rarely been seriously considered that it might be damage to some structure in the ventromedial quadrant of the temporal lobe other than the hippocampus that is responsible for the amnesia. The amygdala and entorhinal area have been ruled out by both the human and animal data. However, the temporal stem is a likely possibility. Its position makes it vulnerable to the surgical approach which was used in human medial temporal lobectomies, and its damage in animals produces deficits in learning and retention. When medial temporal lesions were made in monkeys in the same way that they were made in humans, inadvertent damage to the temporal stem occurred along with the intended amygdaloid and hippocampal injury. Symptoms characteristic of damage to the temporal cortex resulted from these lesions and they were probably caused by the damage to the stem. We sectioned the stem without damaging the hippocampus and produced severe learning and retention deficits.

The stem contains fibre tracts connecting the temporal cortex and amygdala to subcortical structures, but contains no hippocampal connections. Since the amygdala has been ruled out, this relates the amnesia from medial temporal lesions to the temporal cortex rather than the hippocampus, a suggestion originally made by Penfield as an outcome of his observations on stimulation of the temporal cortex. Confirmed instances of lesions of temporal cortex in humans are rare and difficult to interpret, but do not contradict this suggestion. Lesions of temporal cortex in monkeys produce severe cognitive disorders that are reasonably described as perceptual and associative deficits. There is considerable Aristotelean controversy over the words used to describe these deficits in monkeys, but operationally, they are problems in the acquisition and retention of learned tasks.

The patient H. M. probably does have a hippocampal lesion along with his stem damage. Perhaps his spatial disorientation is related to this damage; difficulties in learning and memory deficits displayed by human amnestics are much more general and are more like the effects of lesions of temporal cortex than of hippocampus. The major difference between medial temporal and temporal cortical lesions appears to be that large lesions of temporal cortex produce a more severe and even more general cognitive defect than medial temporal lobectomies. With the temporal stem injury created by the medial temporal lobectomies, there are many connections to the temporal cortex left intact that could account for the difference.

Any or all of the temporal lobe connections that lie within the injured stem could be responsible for the observed memory deficits, but I chose to emphasize the connection to the medial magnocellular part of the medialis dorsalis nucleus because of the suggestion that pathology in this nucleus may be responsible for the amnesia of Korsakoff's psychosis. The high incidence of disease of the mammillary bodies in these patients and the relationship of the mammillary bodies to the hippocampus has provided a major source of support for the hippocampal memory hypothesis. However, the amnesia does not always appear in Korsakoff's patients who have diseased mammillary bodies, and evidence has been presented which suggests that the amnesia is associated with medial thalamic injury. There are a number of instances of amnesia in humans with medial thalamic lesions caused by diseases other than Korsakoff's psychosis and there is experimental evidence of learning and memory deficits produced in animals with such lesions. In contrast, there is no evidence in animals of learning or memory defects produced by lesions of the mammillary bodies.

We should not however, neglect the other connections within the temporal stem. They are all concerned in some way with temporal lobe function and all of them, either alone or in combination, could be responsible for the amnestic effects of medial temporal lesions. Besides the connections to the thalamus, there are massive connections to the basal ganglia and orbitofrontal cortex that should be explored.

No attempt has been made here to explain why cutting this fibre tract should produce the amnestic syndrome. Presumably an important afferent or efferent pathway of the temporal cortex which is involved in storage or retrieval of information, or coding for storage, was damaged by the stem lesion. It is important to remember that complete temporal lobectomy does not abolish the ability to learn or remember but does severely disrupt such processes. Evidently the temporal lobe is a useful tool for such functions, but not a necessary one.

It cannot be said that definitive and final proof has been presented implicating the temporal stem and cortex in human amnesia; its culpability or innocence must ultimately be decided at the pathologist's bench. This paper should provide a clear view of the observations that must be made to resolve the problem finally. Also, we must be alert to the probability that there are amnesias other than those discussed here, taking different forms and involving different, as yet unsuspected, brain areas. Furthermore, we should not be surprised to find memory functions for the hippocampus even though its destruction is probably not responsible for the symptoms of medial temporal amnesia. It is important to maintain a distinction between the putative functions of brain areas and the symptoms of their destruction.

ACKNOWLEDGEMENTS

I wish to thank Drs. Robert L. Isaacson, Leonard E. Jarrard, E. G. Keating, Mortimer Mishkin, David S Olton and Dennis J. Stelzner for their helpful criticism and advice. I also wish to thank Mrs. Nancy Wood for her work on the manuscript.

REFERENCES

ADAMS, J. E. and RUTKIN, B. B. (1970) Visual responses to subcortical stimulation in the visual and limbic system. *Confinia Neurologica*, **32**, 158–164.

ADEY, W. R., KADO, R. T., DIDIO, J. and SCHINDLER, W. J. (1963) Impedance changes in cerebral tissue accompanying a learned discrimination performance in the cat. *Experimental Neurology*, **7**, 259–281.

AKELAITIS, A. J. (1943) Studies on the corpus callosum. VII. Study of language functions (tactile and visual lexia and graphia) unilaterally following section of the corpus callosum. *Journal of Neuropathology and Experimental Neurology*, **2**, 226–262.

AKERT, K. (1964) Comparative anatomy of frontal cortex and thalamofrontal connections. In: *The Frontal Granular Cortex and Behavior*. Edited by J. M. Warren and K. Akert. New York: McGraw Hill, pp. 372-394.

—— GRUESEN, R. A., WOOLSEY, C. N. and MEYER, D. R. (1961) Klüver-Bucy syndrome in monkeys with neocortical ablations of temporal lobe. *Brain*, **84**, 480–498.

ANDERSON, K. V. and SYMMES, D. (1969) The superior colliculus and higher visual functions in the monkey. *Brain Research, Amsterdam*, **13**, 37-52.

BARBIZET, J. (1963) Defect of memorizing of hippocampal-mammillary origin: a review. *Journal of Neurology, Neurosurgery and Psychiatry*, **26**, 127-135.

BEEVOR, C. E. (1909) On the distribution of the different arteries supplying the human brain. *Philosophical Transactions of the Royal Society, B*, **200**, 1-55.

BENSON, F. D., MARSDEN, C. D. and MEADOWS, J. C. (1974) The amnesic syndrome of posterior cerebral artery occlusion. *Acta Neurologica Scandinavica*, **50**, 133-145.

BERGER, T. W., ALGER, B. and THOMPSON, R. F. (1976) Neuronal substrate of classical conditioning in the hippocampus. *Science*, **192**, 483–488.

BICKFORD, R. G., MULDER, D. W., DODGE, H. W., SVIEN, H. J. and ROME, H. P. (1958) Changes in memory function produced by electrical stimulation of the temporal lobe in man. *Research Publications Association for Research in Nervous and Mental Diseases*, **36**, 227-243.

BRIERLEY, J. B., CORSELLIS, J. A. N., HIERONS, R. and NEVIN, S. (1960) Subacute encephalitis of later adult life mainly affecting the limbic areas. *Brain*, **83**, 357-368.

BRION, S., PRAGIER, R., GUÉRIN, R. and TEITGEN, M. (1969) Syndróme de Korsakoff par ramollissement bilatéral du fornix. Le problèm des syndromes amnésiques par lésion vasculaire unilatérale. *Revue Neurologique*, **120**, 255-262.

BROWN, S. and SCHAFER, E. A. (1888) An investigation into the functions of the occipital and temporal lobes of the monkey's brain. *Philosophical Transactions of the Royal Society, London*, **179**, 303-329.

BUERGER, A. A., GROSS, C. G. and ROCHA-MIRANDA, C. E. (1974) Effects of ventral putamen lesions on discrimination learning by monkeys. *Journal of Comparative Physiological Psychology*, **86**, 440–446.

BUTTER, C. M., MCDONALD, J. A. and SNYDER, D. (1969) Orality, preference behavior and reinforcement value of nonfood object in monkeys with orbital frontal lesions. *Science*, **164**, 1306–1308.

CAIRNS, H. and MOSBERG, W. H. (1951) Colloid cyst of the third ventricle *Surgery, Gynecology and Obstetrics*, **92**, 545-570.

CHALUPA, L. M., COYLE, R. S. and LINDSLEY, D. B. (1976) Effect of pulvinar lesions on visual pattern discrimination in monkeys. *Journal of Neurophysiology*, **39**, 354–369.

CHAPMAN, L. F., WALTER, R. D., MARKHAM, C. H., RAND, R. W. and CRANDALL, P. H. (1967) Memory changes induced by stimulation of hippocampus or amygdala in epilepsy patients with implanted electrodes. *Transactions of the American Neurological Association*, **92**, 50–56

CHOW, K. L. (1954) Lack of behavioral effects following destruction of some thalamic association nuclei in monkey. *AMA Archives of Neurology and Psychiatry*, **71**, 762–771.

—— (1961) Effect of local electrographic after-discharges on visual learning and retention in monkey. *Journal of Neurophysiology*, **24**, 391–400.

CHOW, K. L. and RANDALL, W. (1964) Learning and retention in cats with lesions in reticular formation. *Psychonomic Science*, **1**, 259–260.

—— and SURVIS, J. (1958) Retention of overlearned visual habit after temporal cortical ablation in monkey. *AMA Archives of Neurology and Psychiatry*, **79**, 640–646.

CORDEAU, J. P. and MAHUT, H. (1964) Some long-term effects of temporal lobe resections on auditory and visual discrimination in monkeys. *Brain*, **87**, 177–188.

CORRELL, R. E. and SCOVILLE, W. B. (1965*a*) Effects of medial temporal lesions on visual discrimination performance. *Journal of Comparative and Physiological Psychology*, **60**, 175–181.

—— —— (1965*b*) Performance on delayed match following lesions of medial temporal lobe structures. *Journal of Comparative and Physiological Psychology*, **60**, 360–367.

CORSELLIS, J A. N. (1970) The limbic areas in Alzheimer's disease and in other conditions associated with dementia. In: *Alzheimer's Disease and Related Conditions.* A Ciba Foundation Symposium. Edited by G. E. Wolstenholme and Maeve O'Connor, London: J. A. Churchill, pp. 37–45.

—— GOLDBERG, G. J. and NORTON, A. R. (1968) 'Limbic encephalitis' and its association with carcinoma. *Brain*, **91**, 481–498.

COWEY, A. and GROSS, C. G. (1970) Effects of foveal prestriate and inferotemporal lesions on visual discrimination by rhesus monkeys *Experimental Brain Research*, **11**, 128–144.

CRITCHLEY, M. (1930) The anterior cerebral artery and its syndromes. *Brain*, **53**, 120–165.

DAHL, D., INGRAM, W. R. and KNOTT, J. R. (1962) Diencephalic lesions and avoidance learning in cats. *Archives of Neurology*, **7**, 314–319.

DEARMOND, S. J., FUSCO, M. M. and DEWEY, M. M. (1976) *Structure of the Human Brain.* Second edition, New York: Oxford University Press.

DEAN, P. (1974) The effect of inferotemporal lesions on memory for visual stimuli in rhesus monkeys. *Brain Research, Amsterdam*, **77**, 451–469.

—— and WEISKRANTZ, L. (1974) Loss of preoperative habits in rhesus monkeys with inferotemporal lesions: Recognition failure or relearning deficit? *Neuropsychologia*, **12**, 299–311.

DELACOUR, J (1971) Effects of medial thalamic lesions in the rat. A review and an interpretation. *Neuropsychologia*, **9**, 157–174

—— (1977) Cortex inférotemporal et mémoire visuelle à court terme chez le singe. Nouvelles données. *Experimental Brain Research*, **28**, 301–310.

DESTRADE, C., SOUMIREU-MOURAT, B. and CARDO, B. (1973) Effects of post-trial hippocamal stimulation on acquisition of operant behavior in the mouse. *Behavioral Biology*, **8**, 713–724.

DIVAC, I., ROSVOLD, H. E. and SCHWARCBART, M. K. (1967) Behavioral effects of selective ablation of the caudate nucleus. *Journal of Comparative and Physiological Psychology*, **63**, 184–190.

DOTT, N. M. (1938) Surgical aspects of the hypothalamus. In: *The Hypothalamus: Morphological, Functional and Clinical Aspects.* Edited by W. E. Clark. Edinburgh: Oliver and Boyd, pp. 131–185.

DOTY, R. W. and OVERMAN, W. H. (1977) Mnemonic role of forebrain commissures in *macaques.* In: *Laterilization in the Nervous System.* Edited by S. Harnad, R. W. Doty, L. Goldstein, J. Jaynes and G. Krauthaner. New York: Academic Press, pp. 75–88.

DOUGLAS, R. J (1967) The hippocampus and behavior. *Psychological Bulletin*. **67**, 416–422.

DOWNER, J. W. DE C. (1961) Changes in visual gnostic functions and emotional behaviour following unilateral temporal pole damage in the 'split-brain' monkey. *Nature, London*, **191**, 50-51.

GAFFAN, D. (1974) Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *Journal of Comparative and Physiological Psychology*, **86**, 1100–1109.

GARCIA-BENGOCHEA, F., DELATTORE, D., ESQUIVEL, O., VIETA, R. and CLAUDIO, F. (1954) The section of the fornix in the surgical treatment of certain epilepsies. *Transactions of the American Neurological Association*, **79**, 176–178.

GESCHWIND, N. (1965) Disconnexion syndromes in animals and man. I. *Brain*, **88**, 237-294.

—— and FUSILLO, M. (1966) Color-naming defects in association with alexia. *Archives of Neurology*, **15**, 137-146.

GLEES, P. and GRIFFITH, H. B. (1952) Bilateral destruction of the hippocampus (*Cornu Ammonis*) in a case of dementia. *Monatsschrift für Psychiatrie und Neurologie*, **123**, 193-204.

GOL, A. and FAIBISH, G. M. (1967) Effects of human hippocampal ablation. *Journal of Neurosurgery*, **26**, 390–398.

GOLD, P. E., MACRI, J. and MCGAUGH, J. L. (1973) Retrograde amnesia produced by subseizure amygdala stimulation. *Behavioral Biology*, **9**, 671-680.

GOLDBERG, H. I. (1974) The anterior choroidal artery. In: *Radiology of the Skull and Brain*. Edited by T. H. Newton and D. G. Potts. St. Louis: C. V. Mosby. Vol. 2, Book 2, pp. 1628-1658.

GROSS, C. G. (1972) Visual functions of inferotemporal cortex. In: *Handbook of Sensory Physiology*. Edited by R. Jung. Heidelberg and New York: Springer-Verlag, pp. 451-482.

—— COWEY, A. and MANNING, F. J. (1971) Further analysis of visual discrimination deficits following foveal prestriate and inferotemporal lesions in rhesus monkeys. *Journal of Comparative and Physiological Psychology*, **76**, 1-7.

GUILLERY, R. W. (1959) Afferent fibres to the dorso-medial thalamic nucleus in the cat. *Journal of Anatomy, London*, **93**, 403–419.

HARLOW, H. F., DAVID, R. T., SETTLAGE, P. H. and MEYER, D. R. (1952) Analysis of frontal and posterior association syndromes in brain-damaged monkeys. *Journal of Comparative and Physiological Psychology*, **45**, 419–429.

HASSLER, R. and RIECHERT, T. (1957) Uber einen fall von doppelseitiger fornicotomie bei sogennanter temporaler epilepsie. *Acta Neurochirurgica*, **5**, 330–340.

HEILMAN, K. and SYPERT, G. W. (1977) Korsakoff's syndrome resulting from bilateral fornix lesions. *Neurology, Minneapolis*, **27**, 490–493.

HOREL, J. A. and KEATING, E. G. (1969) Partial Klüver-Bucy syndrome produced by cortical disconnection. *Brain Research, Amsterdam*, **16**, 281-284.

—— —— (1972) Recovery from a partial Klüver-Bucy syndrome in the monkey produced by disconnection. *Journal of Comparative and Physiological Psychology*, **79**, 105-114.

—— —— and MISANTONE, L. G. (1975) Partial Klüver-Bucy syndrome produced by destroying temporal neocortex or amygdala. *Brain Research, Amsterdam*, **94**, 347-359.

—— and MISANTONE, L. G. (1974) The Klüver-Bucy syndrome produced by partial isolation of the temporal lobe. *Experimental Neurology*, **42**, 101-112.

HOREL, J. A. and MISANTONE, L. G. (1976) Visual discrimination impaired by cutting temporal lobe connections. *Science*, **193**, 336–338.

ISAACSON, R. L. (1972) Hippocampal destruction in man and other animals. *Neuropsychologia*, **10**, 47–64.

IVERSEN, S. (1976) Do hippocampal lesions produce amnesia in animals? In: *International Review of Neurobiology*. Edited by C. C. Pfeiffer and J. R. Smythies. New York: Academic Press. Vol. 19, pp. 1–49.

—— and MISHKIN, M. (1973) Comparison of superior temporal and inferior prefrontal lesions on auditory and non-auditory tasks in rhesus monkeys. *Brain Research, Amsterdam*, **55**, 355–367.

—— and WEISKRANTZ, L. (1964) Temporal lobe lesions and memory in the monkey. *Nature, London*, **201**, 740–742.

IWAI, E. and MISHKIN, M. (1968) Two visual foci in the temporal lobe of monkeys. Japan-U.S. Joint Seminar on Neurophysiological Basis of Learning and Behavior.

—— —— (1969) Further evidence on the locus of the visual area in the temporal lobe of the monkey. *Experimental Neurology*, **25**, 585–594.

JARRARD, L. E. (1973) The hippocampus and motivation. *Psychological Bulletin*, **79**, 1–12.

—— (1978) Selective hippocampal lesions. Differential effects on performance of a spatial task with preoperative vs. postoperative training. *Journal of Comparative and Physiological Psychology*. In press.

JASPER, H. and RASMUSSEN, T. (1958) Studies of clinical and electrical response to deep stimulation in men, with some considerations of functional anatomy. *Research Publication Association for Research in Nervous and Mental Diseases*, **36**, 316–334.

JOHN, E. R. (1972) Switchboard versus statistical theories of learning and memory. *Science*, **177**, 850–864.

—— and KILLAM, K. F. (1960) Electrophysiological correlates of differential approach-avoidance conditioning in cats. *Journal of Nervous and Mental Diseases*, **131**, 183–201.

JONES, B. and MISHKIN, M. (1972) Limbic lesions and the problem of stimulus-reinforcement associations. *Experimental Neurology*, **36**, 362–377.

KEATING, E. G. (1976) Effects of tectal lesions on peripheral field vision in the monkey. *Brain Research, Amsterdam*, **104**, 316–320.

—— and HOREL, J. A. (1971) Somatosensory deficit produced by parietal-temporal disconnection in the monkey. *Experimental Neurology*, **33**, 547–565.

—— —— (1972) Effects of prestriate and striate lesions on performance of simple visual tasks. *Experimental Neurology*, **35**, 322–336.

KESNER, R. P. and DOTY, R. W. (1968) Amnesia produced in cats by local seizure activity initiated from the amygdala. *Experimental Neurology*, **21**, 58–68.

KIM, C., CHANG, H. K. and CHU, J. W. (1967) Consequences of ablating mammillary bodies in dogs. *Journal of Comparative and Physiological Psychology*, **63**, 469–476.

KIMBLE, D. P. (1968) Hippocampus and internal inhibition. *Psychological Bulletin*, **70**, 285–295.

KLINGLER, J. and GLOOR, P. (1960) The connections of the amygdala and of the anterior temporal cortex in the human brain. *Journal of Comparative Neurology*, **115**, 333–369.

KLÜVER, H. and BUCY, P. C. (1938) An analysis of certain effects of bilateral temporal lobectomy in the rhesus monkey with special reference to 'psychic blindness'. *Journal of Psychology*, **5**, 33-54.

—— —— (1939) Preliminary analysis of functions of the temporal lobes in monkeys. *Archives of Neurology and Psychiatry*, **42**, 979-1000.

LEONARD, C. M. (1972) The connections of the dorsomedial nuclei. *Brain Behavior Evolution*, **6**, 524-541.

McDONOUGH, J. A. and KESNER, R. P. (1971) Amnesia produced by brief electrical stimulation of the amygdala or dorsal hippocampus in cats. *Journal of Comparative and Physiological Psychology*, **77**, 171-178.

McENTEE, W. J., BIBER, M. P., PERL, D. P. and BENSON, D. F. (1976) Diencephalic amnesia: a reappraisal. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 436-441.

McLARDY, T. (1970) Memory functions in the hippocampal gyri but not in hippocampus. *International Journal of Neuroscience*, **1**, 113-118.

MAHUT, H. (1971) Spatial and object reversal learning in monkeys with partial temporal lobe ablations. *Neuropsychologia*, **9**, 409-424.

—— (1972) A selective spatial deficit in monkeys after transection of the fornix. *Neuropsychologia*, **10**, 65-74.

—— and CORDEAU, J. (1963) Spatial reversal deficit in monkeys with amygdalohippocampal ablations. *Experimental Neurology*, **7**, 426-434.

MALAMUD, M. and SKILLICORN, S. A. (1956) Relationship between the Wernicke and the Korsakoff syndrome. *AMA Archives of Neurology and Psychiatry*, **76**, 585-596.

MEANS, L. W., HARRELL, T. H., MAYO, E. S. and ALEXANDER, G. B. (1974) Effects of dorsomedial thalamic lesions on spontaneous alternation, maze activity and runway performance in the rat. *Physiology and Behavior*, **12**, 973-979.

MEYER, D. R. (1958) Some psychological determinants of sparing and loss following damage to the brain. In: *Biological and Biochemical Basis of Behavior*. Edited by H. F. Harlow and C. N. Woolsey. Madison: University of Wisconsin Press, pp. 173-192.

MILNER, B. (1970) Memory and the medial temporal regions of the brain. In: *Biology of Memory*. Edited by K. H. Pribram and D. E. Broadbent. New York: Academic Press, pp. 29-50.

—— (1971) Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin*, **27**, 272-277.

—— (1972) Disorders of learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, **19**, 421-446.

—— CORKIN, S. and TEUBER, H.-L. (1968) Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H. M. *Neuropsychologia*, **6**, 215-234.

MISHKIN, M. (1954) Visual discrimination performance following partial ablations of the temporal lobe: II. Ventral surface *vs.* hippocampus. *Journal of Comparative and Physiological Psychology*, **147**, 187-193.

—— (1966) Visual mechanisms beyond the striate cortex. In: *Frontiers in Physiological Psychology*. Edited by R. W. Russell. New York: Academic Press, pp. 93-119.

MISHKIN, M. (1972) Cortical visual areas and their interactions. In: *The Brain and Human Behavior*, Berlin: Springer-Verlag, pp. 187-208.

—— and HALL, M. (1955) Discrimination along a size continuum following ablation of the inferior temporal convexity in monkeys. *Journal of Comparative and Physiological Psychology*, **48**, 97-101.

—— and OUBRE, J. L. (1976) Dissociation of deficits on visual memory tasks after inferior temporal and amygdala lesions in monkeys. *Neuroscience Abstracts*, Vol. II, part 2, p. 1127.

—— and PRIBRAM, K. H. (1954) Visual discrimination performance following partial ablations of the temporal lobe: ventral *vs.* lateral. *Journal of Comparative and Physiological Psychology*, **47**, 14-20.

NATHAN, P. W. and SMITH, M. C. (1950) Normal mentality associated with a maldeveloped 'rhinencephalon'. *Journal of Neurology, Neurosurgery and Psychiatry*, **13**, 191-197.

NAUTA, W. J. H. (1961) Fibre degeneration following lesions of the amygdaloid complex in the monkey. *Journal of Anatomy*, **95**, 515-531.

—— (1962) Neural associations of the amygdaloid complex in the monkey. *Brain*, **85**, 505-520.

—— (1964) Some efferent connections of the prefrontal cortex in the monkey. In: *The Frontal Granular Cortex and Behavior.* Edited by J. M. Warren and K. Akert. New York: McGraw-Hill, pp. 397-409.

—— and MEHLER, W. R. (1966) Projections of the lentiform nucleus in the monkey. *Brain Research, Amsterdam*, **1**, 3-42.

O'KEEFE, J. and DOSTROVSKY, J. (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely moving rat. *Brain Research, Amsterdam*, **34**, 171-175.

—— NADEL, L., KEIGHTLY, S. and KILL, D. (1975) Fornix lesions selectively abolish place learning in the rat. *Experimental Neurology*, **48**, 152-166.

OLDS, J. (1970) The behavior of hippocampal neurons during conditioning experiments. In: *The Neural Control of Behavior.* Edited by R. E. Whalen, R. F. Thompson, M. Verzeano and N. M. Weinberger. New York: Academic Press, pp. 257-293.

OLDS, M. E. and OLDS, J. (1963) Approach-avoidance analysis of rat diencephalon. *Journal of Comparative Neurology*, **120**, 259-295.

OLTON, D. S. and ISAACSON, R. L. (1967) Effects of lateral and dorsomedial thalamic lesions on retention of active avoidance tasks. *Journal of Comparative and Physiological Psychology*, **64**, 256-261.

—— WALKER, J. A. and GAGE, F. H. (1978) Hippocampal connections and spatial discrimination. *Brain Research, Amsterdam*, **139**, 295-308.

ORBACH, J., MILNER, B. and RASMUSSEN, T. (1960) Learning and retention in monkeys after amygdala-hippocampus resection. *Archives of Neurology, Chicago*, **3**, 230-251.

PASSINGHAM, R. E. (1972) Visual discrimination learning after selective prefrontal ablations in monkeys (*Macaca mulatta*). *Neuropsychologia*, **10**, 27-39.

PENFIELD, W. and JASPER, H. H. (1954) *Epilepsy and the Functional Anatomy of the Human Brain.* Boston: Little Brown.

—— and MATHIESON, G. (1974) Memory: Autopsy findings and comments on the role of hippocampus in experiential recall. *Archives of Neurology, Chicago*, **31**, 145-154.

PENFIELD, W. and MILNER, B. (1958) Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Archives of Neurology and Psychiatry*, **79**, 475–497.

—— and ROBERTS, L. (1959) *Speech and Brain Mechanisms*. Princeton: Princeton University Press.

PETERS, R. H., ROSVOLD, H. E. and MIRSKY, A. F. (1956) The effect of thalamic lesions on delayed response-type tests in the rhesus monkey. *Journal of Comparative and Physiological Psychology*, **49**, 111–116.

PETIT-DUTAILLIS, D., CHRISTOPHE, J., PERTUISET, B., DREYFUS-BRISAC, C. and BLANC, C. (1954) Lobectomie temporale bilatérale pour épilepsie. Evolution des perturbations fonctionelles postopératories. *Revue Neurologique*, **91**, 129–133.

PLOOG, D. W. and MACLEAN, P. D. (1963) On functions of mammillary bodies in the squirrel monkey. *Experimental Neurology*, **7**, 76–85.

PRIBRAM, K. H. and BAGSHAW, M. (1953) Further analysis of the temporal lobe syndrome utilizing fronto-temporal ablations. *Journal of Comparative Neurology*, **99**, 347–375.

—— CHOW, K. L. and SEMMES, J. (1953) Limit and organization of the cortical projection from the medial thalamic nucleus in monkey. *Journal of Comparative Neurology*, **98**, 433–448.

—— WILSON, W. A. and CONNORS, J. (1962) Effect of lesions of the medial forebrain on alternation behavior of rhesus monkeys. *Experimental Neurology*, **6**, 36–47.

REITZ, S. L. and PRIBRAM, K. H. (1969) Some subcortical connections of the inferotemporal gyrus of the monkey. *Experimental Neurology*, **25**, 632–645.

ROSENSTOCK, J., FIELD, T. D. and GREENE, E. (1977) The role of mammillary bodies in spatial memory. *Experimental Neurology*, **55**, 340–352.

SABOURAND, O., GAGNEPAIN, J., CHATEL, M. and MENAULT, F. (1976) Un cas de lesions bilaterales de la convexité temporale: tentative de définition des symptomes. *Cortex*, **12**, 154–168.

SANDERS, H. L. and WARRINGTON, E. K. (1971) Memory for remote events in amnesic patients. *Brain*, **94**, 661–668.

SCHMALTZ, L. W. and THEIOS, J. (1972) Acquisition and extinction of a classically conditioned response in hippocampectomized rabbits (*Orictolagus curriculus*). *Journal of Comparative and Physiological Psychology*, **79**, 328–333.

SCHULMAN, S. (1957) Bilateral symmetrical degeneration of the thalamus: clinicopathological study. *Journal of Neuropathology and Experimental Neurology*, **16**, 446–470.

—— (1964) Impaired delayed response from thalamic lesions. *Archives of Neurology, Chicago*, **11**, 477–499.

SCHWARTZBAUM, J. S. (1965) Discrimination behavior after amygdalectomy in monkeys: Visual and somesthetic learning and perceptual capacity. *Journal of Comparative and Physiological Psychology*, **60**, 314–319.

SCOVILLE, W. B. (1954) The limbic lobe in man. *Journal of Neurosurgery*, **11**, 64–66.

—— DUNSMORE, R. H., LIBERSON, W. T., HENRY, C. E. and PEPE, A. (1951) Observations on medial temporal lobotomy and uncotomy in the treatment of psychotic states. Preliminary review of 19 operative cases compared with 60 frontal lobotomy and undercutting cases. *Research Publication Association for Research in Nervous and Mental Diseases*, **31**, 347–369.

—— and MILNER, B. (1957) Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, **20**, 11–21.

SELTZER, B. and BENSON, F. D. (1974) The temporal pattern of retrograde amnesia in Korsakoff's disease. *Neurology, Minneapolis*, **24,** 527-530.

SKINNER, J. E. and LINDSLEY, D. B. (1967) Electrophysiological and behavioral effects of blockade of the nonspecific thalamocortical system. *Brain Research, Amsterdam*, **6,** 95-118.

SMYTHE, G. E. and STERN, K. (1938) Tumours of the thalamus—a clinico-pathological study. *Brain*, **61,** 339-374.

SOLOMON, P. R. and MOORE, J. W. (1975) Latent inhibition and stimulus generalization of the classically conditioned nictitating membrane response in rabbits (*Oryctolagus curriculus*) following dorsal hippocampal ablations. *Journal of Comparative and Physiological Psychology*, **89,** 1192-1203.

SOURANDER, P. and SJÖGREN, H. (1970) The concept of Alzheimer's disease and its clinical implications. In: *Alzheimer's Disease and Related Conditions*. Edited by G. E. W. Wolstenholme and M. O'Connor. London: J. and A. Churchill, pp. 11-32.

SPIEGEL, E. A., WYCIS, H. T., ORCHINIK, L. W. and FREED, H. (1955) The thalamus and temporal orientation. *Science*, **121,** 771-772.

SQUIRE, L. R. and SLATER, P. C. (1976) New learning capacity and remote memory in chronic anterograde amnesia. *Neuroscience Abstracts*, Vol. II, part 1, p. 452.

STAMM, J. S. and ROSEN, S. C. (1971) Learning on somesthetic discrimination and reversal tasks by monkeys with epileptogenic implants in anteromedial temporal cortex. *Neuropsychologia*, **9,** 185-194.

STEPIEN, L. S., CORDEAU, J. P. and RASMUSSEN, T. (1960) The effect of temporal lobe and hippocampal lesions on auditory and visual recent memory in monkeys. *Brain*, **83,** 470-489.

STERN, K. (1939) Severe dementia associated with bilateral symmetrical degeneration of the thalamus. *Brain*, **62,** 157-171.

SULLIVAN, M. and HAMILTON, C. (1973) Memory established via the anterior commissure of monkeys. *Physiology and Behavior*, **11,** 873-879.

SWEET, W. H., TALLAND, G. A. and ERVIN, F. R. (1959) Loss of recent memory following section of fornix. *Transactions of the American Neurological Association*, **84,** 76-82.

TANAKA, D. (1976) Thalamic projections of the dorsomedial prefrontal cortex in the rhesus monkey (*Macaca mulatta*). *Brain Research, Amsterdam*, **110,** 21-38.

TERZIAN, H. and ORE, G. D. (1955) Syndrome of Klüver and Bucy reproduced in man by bilateral removal of the temporal lobes. *Neurology, Minneapolis*, **5,** 373-380.

TEUBER, H. L., MILNER, B. and VAUGHAN, H. G. (1968) Persistent anterograde amnesia after stab wound of the basal brain. *Neuropsychologia*, **6,** 267-282.

THOMPSON, R. F. (1976) The search for the engram. *American Psychologist*, **31,** 209-227.

THOMPSON, R. (1963) Thalamic structures critical for retention of an avoidance conditioned response in rats. *Journal of Comparative and Physiological Psychology*, **56,** 261-267.

—— and MYERS, R. E. (1971) Brainstem mechanisms underlying visually guided responses in the rhesus monkey. *Journal of Comparative and Physiological Psychology*, **74,** 479-512.

UNGERLEIDER, L. G., GANZ, L. and PRIBRAM, K. H. (1977) Size constancy in rhesus monkeys: effects of pulvinar, prestriate and inferotemporal lesions. *Experimental Brain Research*, **27,** 251-269.

VAN BUREN, J. M. and BORKE, R. C. (1972) The mesial temporal substratum of memory. Anatomical study in three individuals. *Brain*, **95**, 599-632.

VAN HOESEN, G. W. and PANDYA, D. N. (1975*a*) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. I. Temporal lobe afferents. *Brain Research, Amsterdam*, **95**, 1-24.

—— —— (1975*b*) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. III. Efferent connections. *Brain Research, Amsterdam*, **95**, 39-59.

VAN WAGENEN, W. P. and HERREN, R. Y. (1940) Surgical division of commissural pathways in the corpus callosum. *Archives of Neurology and Psychiatry*, **44**, 740-759.

VANDERWOLF, C. H. (1969) Effects of medial thalamic damage on initiation of movement and learning. *Psychonomic Science*, **17**, 23-24.

VICTOR, M., ADAMS, R. D. and COLLINS, G. H. (1971) *The Wernicke-Korsakoff Syndrome*. Philadelphia: F. A. Davis.

—— ANGEVINE, J. B., MANCALL, E. L. and FISHER, C. M. (1961) Memory loss with lesions of the hippocampal formation. *Archives of Neurology, Chicago*, **5**, 244-263.

WARREN, J. M. and AKERT, K. (1960) Impaired problem solving by cats with thalamic lesions. *Journal of Comparative and Physiological Psychology*, **53**, 207-211.

WEISKRANTZ, L. and COWEY, A. (1963) Striate cortex lesions and visual acuity of the rhesus monkey. *Journal of Comparative and Physiological Psychology*, **56**, 225-231.

WHITLOCK, D. G. and NAUTA, W. J. H. (1956) Subcortical projections from the temporal neocortex in Macaca mulatta. *Journal of Comparative and Physiological Psychology*, **56**, 183-212.

WILLIAMS, M. and PENNYBACKER, J. (1954) Memory disturbances in third ventricle tumours. *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 115-123.

WOODY, C. D. and ERVIN, F. R. (1966) Memory function in cats with lesions of the fornix and mammillary bodies. *Physiology and Behavior*, **1**, 273-280.

WOOLSEY, R. M. and NELSON, J. S. (1975) Asymptomatic destruction of the fornix in man. *Archives of Neurology, Chicago*, **32**, 566-568.

YAHR, M. D., DUVOISIN, R. C and COWEN, D. (1965) Encephalopathy associated with carcinoma. *Transactions of the American Neurological Association*, **90**, 80-86.

ZEKI, S. M. (1973) Comparison of the cortical degeneration in the visual regions of the temporal lobe of the monkey following section of the anterior commissure and the splenium. *Journal of Comparative Neurology*, **148**, 167-176.

ZORNETZER, S. F., BOAST, C. and HAMRICK, M. (1974) Neuroanatomic localization and memory processing in mice: The role of the dentate gyrus of the hippocampus. *Physiology and Behavior*, **13**, 569-575.

(*Received July 26, 1977*)

Brain (1978), **101**, 447–460

ELECTROENCEPHALOGRAPHIC STUDIES OF MYOCLONUS

MYOCLONUS-RELATED CORTICAL SPIKES AND HIGH AMPLITUDE SOMATOSENSORY EVOKED POTENTIALS

by HIROSHI SHIBASAKI, YORIAKI YAMASHITA *and*
YOSHIGORO KUROIWA

(*From the Department of Neurology, Neurological Institute, Faculty of Medicine, Kyushu University 60, Fukuoka City 812, Japan*)

INTRODUCTION

SPIKE-AND-WAVE complex in association with myoclonus was first reported by Grinker, Serota and Stein (1938). Since then, polygraphic studies of the spontaneously occurring myoclonus and of the electroencephalogram (EEG) in man have been performed by many investigators using an electroencephalograph or cathode ray oscillograph (Dawson, 1946; Haguenau, Christophe, Rémond and Pecker, 1950; Van Bogaert, Radermecker and Titeca, 1950; Gastaut and Rémond, 1952; Bradshaw, 1954; Harriman and Millar, 1955; Lance and Adams, 1963; Halliday, 1967*a*, *b*; Kuroiwa, Ohta, Kato and Inoue, 1968; Hambert and Petersén, 1970; Shibasaki, Logothetis and Torres, 1971; Shibasaki, Kato and Kuroiwa, 1973). By the conventional polygraphic technique, however, it has often been difficult to evaluate the relationship between the myoclonic discharge and EEG paroxysms. The authors succeeded in recording the EEG correlates of myoclonus, which were not recognizable on the routine polygraphic recordings, by averaging the EEG time-locked to the following myoclonic discharge (Shibasaki and Kuroiwa, 1975). Recently Hallett, Chadwick, Adam and Marsden (1977) used the same technique in their patient with post-hypoxic myoclonus, but detected no myoclonus-related spike.

Dawson (1947) found an extremely high amplitude somatosensory evoked potential in a patient with myoclonic epilepsy. This high amplitude SEP was demonstrated in patients with progressive myoclonic epilepsy, but not in those with essential myoclonus (Halliday and Halliday, 1970; Halliday, 1975). Some patients, whose myoclonus can be elicited by electrical stimulation of the peripheral nerve at the time of recording SEP, were of especial interest to various investigators (Watson and Denny-Brown, 1955; Halliday, 1967*b*; Pagni, Marossero, Cabrini, Ettorre and Infuso, 1971; Sutton and Mayer, 1974; Sutton, 1975; Engel, Rapin and Giblin, 1977; Rosén, Fehling, Sedgwick and Elmqvist, 1977; Hallett, Chadwick, Adam and Marsden, 1977). In spite of these extensive studies, the physiological mechanism underlying this high amplitude SEP remains undetermined.

This paper aims at reporting on the following two studies. First, in order to confirm our previous results, which were based on a rather small number of patients (Shibasaki and Kuroiwa, 1975), and to contribute to better classification of myoclonus, the technique of jerk-locked averaging was applied to a larger number of patients with various kinds of myoclonus. Secondly, some characteristics of the high amplitude SEP were studied to see whether it is just an exaggerated response of the sensory cortex to stimulation or not. Discussion will be focused on a possible relationship between the high amplitude SEP and the myoclonus-related cortical spike demonstrated by the jerk-locked averaging technique.

SUBJECTS

Subjects were 30 patients, 14 males and 16 females, who presented with various kinds of myoclonus. The age of the patients at the time of examination ranged from 14 to 60 years. They were classified into 6 diagnostic groups; 14 patients with progressive myoclonic epilepsy, 3 suffering from 'epilepsy with myoclonus', 4 with essential myoclonus, 2 with subacute spongiform encephalopathy (SSE), 2 with midbrain infarction and 5 with other conditions. Among the 14 patients with progressive myoclonic epilepsy, 6 showed clinical evidence of cerebellar ataxia compatible with 'dyssynergia cerebellaris myoclonica' or Ramsay Hunt syndrome. Three patients suffering from 'epilepsy with myoclonus' had generalized convulsive seizures and intermittent non-progressive myoclonus. Essential myoclonus was defined as non-progressive myoclonus without any associated convulsive seizures, mental impairment or other neurological deficits. One of the 2 patients with subacute spongiform encephalopathy had an autopsy-proven Creutzfeldt-Jakob syndrome, although the EEG did not show periodic sharp discharges at least during wakefulness. The other showed classical periodic sharp discharges on the routine EEG. Two patients with unilateral midbrain infarction exhibited myoclonus of the contralateral upper extremity in addition to Benedikt's syndrome. Four of 5 patients classified as having other conditions were thought to have cerebral degenerative diseases of unclassified type and one had probable cerebrovascular disease of undetermined nature.

METHODS

All electroencephalographic studies were performed in a dimly-lit, shielded room. The subject lay on a bed or sat in a chair, and the eyes were kept gently closed during the study.

The routine EEG was recorded by placing pad electrodes on the scalp according to the 10–20 system. The frequency response of the whole electroencephalograph, including the pen-writer, was 3 dB down at 1·3 and 80 Hz. Both bipolar and referential derivations were used. In the referential derivation, the ipsilateral ear electrode served as a reference.

For the polygraphic recording, the scalp electrodes were placed on the central (C3 and C4) and adjacent areas according to the 10–20 system. Both bipolar and referential derivations were used. For the referential derivation, the linked ear electrode served as a reference. The EMG was recorded by a pair of surface disc electrodes placed 3 cm apart over a muscle of the upper extremity, which was showing frequent myoclonic contractions. When the spontaneous myoclonus was rare, the extremity was held in the position in which myoclonic jerks occurred most frequently. Both the EEG and EMG were amplified and written with a San-ei electroencephalograph 1A52 with a paper speed of 3 and 6 cm/s. The frequency response of the electroencephalograph including the pen-writer was 3 dB down at 1·3 and 80 Hz both for the EEG and EMG. The frequency response of the amplifier was 10 per cent down at 1 and 2,000 Hz.

For the jerk-locked averaging, the EMG onset, recorded with surface electrodes, was converted to a pulse by a Nihonkohden pulse converter. The EEG, EMG and the EMG pulse were recorded on a FM magnetic tape. Analysis of the data was carried out by averaging 50 to 200 samples of the EEG and an equal number of the EMG samples, time-locked to the EMG pulse, by a San-ei CNV Program AV-C. This is an averaging program consisting of two channels. In the first channel, the averager operated by memorizing input samples continuously in 200 address. On being triggered by an EMG pulse, coincident with the myoclonic jerk, it transferred the preceding 100 address from the first channel to the second channel. In the second channel, the data were averaged in addition to further 100 address following the pulse. Thus, the samples both preceding and following the EMG pulse could be averaged in the same experiment. Samples associated with any obvious artifact were omitted from averaging. Random averaging of each EEG tracing was obtained as a control. The results were written out on an X-Y recorder. The tests were repeated at least twice a day, and in most subjects on different days

To obtain the SEP, the median nerve was electrically stimulated with a pair of surface electrodes placed 3 cm apart just proximal to the wrist. A square wave pulse of 0·5 ms duration was produced by a San-ei stimulator. The stimulus intensity was adjusted to 10 to 15 per cent above the threshold for contraction of the opponens pollicis muscle in each subject. The rate of stimulation was controlled manually to produce an approximately random interstimulus interval of between 1 and 3 seconds. Scalp electrodes were normally placed 7 cm lateral and 2 cm posterior to the vertex, but additional electrodes were also used to study the distribution of the SEP. Both bipolar and referential derivations were used. For the latter, the linked ear electrode served as a reference. The EEG was amplified with the San-ei electroencephalograph 1A52. The frequency response of its amplifier was 10 per cent down at 1 and 2,000 Hz. In some subjects, the surface EMG was recorded from the corresponding thenar muscle in order to detect a long-loop reflex. The EEG, EMG and the stimulus pulse were recorded on a FM magnetic tape. Seventy-four stimulations composed one session, and more than two sessions were given for each test. Analysis of the data was accomplished by averaging the responses to 64 stimuli, time-locked to the stimulus pulse, with a San-ei Signal Processor 7SO6. Analysis time ranged from 80 to 400 ms after the stimulus pulse. Samples associated with any artifact were omitted. The results were written out on an X-Y recorder.

RESULTS

(1) *Paroxysmal EEG Abnormalities*

In the routine EEG records, diffuse, bilateral spike-and-wave complexes or bursts were recognized in the majority of patients with progressive myoclonic epilepsy and 'epilepsy with myoclonus' (Table 1). Among 13 patients with other diagnoses, on the other hand, only one showed spike-and-wave complexes. This patient had status epilepticus and myoclonic jerks probably on the basis of a cerebrovascular disease. A patient with progressive myoclonic epilepsy, who did not show spike-and-wave complexes, showed only rare occurrences of 6 Hz phantom spike-and-waves.

TABLE 1. PAROXYSMAL EEG ABNORMALITIES IN PATIENTS WITH MYOCLONUS

	Spike-and-wave burst	*Others*	*None*	*Total*
Progressive myoclonic epilepsy	13	1	0	14
Epilepsy with myoclonus	3	0	0	3
Essential myoclonus	0	1	3	4
Subacute spongiform encephalopathy	0	2	0	2
Midbrain infarction	0	0	2	2
Others	1	0	4	5
Total	17	4	9	30

(2) *Polygraphic Recordings*

Among 17 patients who showed spike-and-wave complexes or bursts on the routine EEG, only 5 patients showed myoclonic jerks occurring at times more or less synchronously with the spike-and-wave complexes on the conventional polygraphic recordings. The temporal relationship between the cortical spike and the myoclonus in these 5 patients varied. Some myoclonic jerks were preceded by the cortical spike, but others were even followed by the spike. An example is shown in fig. 1.

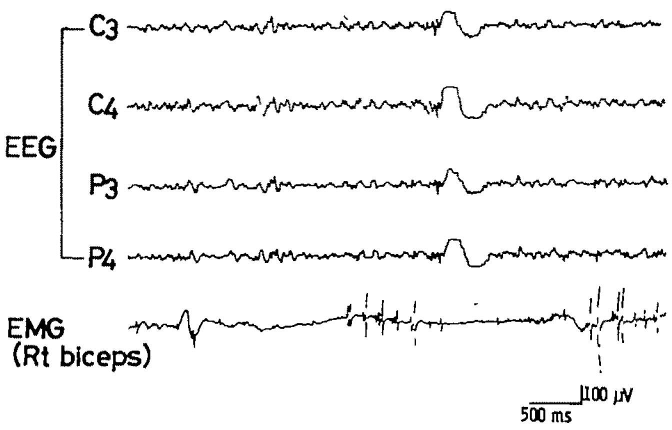


FIG. 1. Polygraph of a 34-year-old male with progressive myoclonic epilepsy. EEGs were recorded in reference to the linked ear electrode. Frequent myoclonic discharges are seen in the right biceps muscle, but most of them are independent of visible cortical spikes.

(3) *Jerk-locked Averaging*

Results of the jerk-locked averaging are summarized in Table 2. In all patients with progressive myoclonic epilepsy, in which this technique was applicable, positive-negative, biphasic, sharp potentials, either followed or not followed by a negative slow wave, were demonstrated in close temporal relationship with the

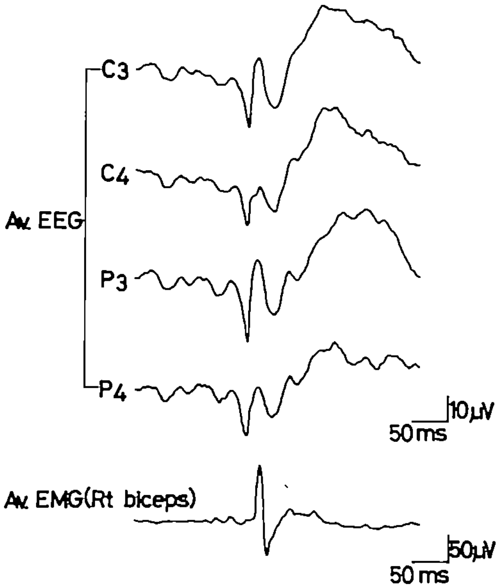


FIG. 2. Jerk-locked averaging of the EEG and EMG in the same patient as in fig 1. Sharp, positive-negative, biphasic potentials followed by a large slow wave are seen with larger amplitude over the left hemisphere, time-locked to the myoclonic discharge from the right biceps muscle. Upward deflection denotes negativity in all figures in this paper.

myoclonic EMG discharge (fig. 2). The second, negative-going phase of the biphasic potential is here called the spike potential. The amplitude of this spike, which was defined as a height from the preceding positive peak to the peak of the spike, ranged from 5 to 27 μV with the mean of 13 μV, and its duration, the time interval between the preceding positive peak and the following positive peak, was 20 to 40 ms with a mean of 32 ms. In all these cases, the myoclonus-related spike or spike-and-wave was seen with larger amplitude over the hemisphere contralateral to the myoclonus. All of these myoclonus-related spikes preceded the onset of the myoclonic discharge. The time interval from the onset (the preceding positive peak) of the cortical spike to the myoclonic EMG of a contralateral upper extremity muscle ranged from 7 to 15 ms. None of the 3 patients with essential myoclonus showed cortical spikes in relation to the myoclonic jerks, and no patient of other categories showed myoclonus-related spikes. In the 2 patients with subacute spongiform encephalopathy, the technique of jerk-locked averaging demonstrated a sharp wave in close temporal relationship with the myoclonic jerk. One of these patients without periodic sharp discharges on the routine EEG showed a sharp wave of about 15 μV and 100 ms duration on the contralateral central area with the present technique. In the other patient with subacute spongiform encephalopathy, who showed periodic sharp discharges in association with myoclonic jerks on the conventional polygraphic tracings, the averaged recording demonstrated a focus of the periodic sharp discharge at the centro-parietal area contralateral to the myoclonus. The onset of these sharp waves preceded onset of the myoclonus by 50 to 280 ms.

TABLE 2. MYOCLONUS-RELATED CORTICAL ACTIVITIES BY JERK-LOCKED AVERAGING

	Cases	*Spike*	*Sharp wave*	*Interval* (*EEG–EMG*)
Progressive myoclonic epilepsy	7	7	0	7–15 ms
Essential myoclonus	3	0	0	
Subacute spongiform encephalopathy	2	0	2	50–280 ms
Midbrain infarction	1	0	0	
Others	2	0	1	100 ms

(4) *Somatosensory Evoked Potential* (*SEP*)

In 13 of 14 patients with progressive myoclonic epilepsy, the somatosensory evoked potential showed a uniform abnormality characterized by an extremely high amplitude, positive-negative, biphasic waves followed by a high amplitude, negative slow wave. The initial high amplitude negative wave corresponded to N33 component of the normal SEP (Shibasaki, Yamashita and Tsuji, 1977) as far as its latency was concerned, and therefore it is called here N33. The amplitude of the N33 ranged from 12 to 75 μV (mean 41 μV), and its period from 20 to 47 ms (mean 36 ms). The mean amplitude of N33 component in normal subjects was 2·4 μV (Shibasaki, Yamashita and Tsuji, 1977). The N20 component of progressive myoclonic epilepsy patients appeared the same as that of the normal SEP both as to its latency and amplitude. The abnormal SEP in these patients usually lacked the component corresponding to the N62 of the normal SEP (fig. 3). The high amplitude SEP was not demonstrated in any of 14 patients belonging to other groups of myoclonus.

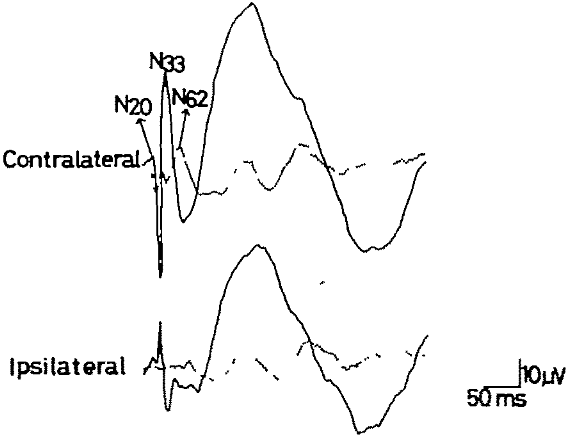


FIG. 3. SEP in response to electrical stimulation of the median nerve just proximal to the wrist in a 17-year-old male with progressive myoclonic epilepsy In contrast with the SEP of a normal control, drawn in a dotted line, the N33 component is extremely large, and the component corresponding to N62 is lacking.

(5) *Long Loop Reflex*

A long loop reflex was recorded in 8 patients with progressive myoclonic epilepsy. In these patients, the stimuli to the median nerve provoked clinically visible myoclonic jerks of varying amplitude. In 4 of these patients, the long loop reflex was demonstrated not only in the thenar muscle of the stimulated side but also in that of the non-stimulated side (fig. 4). Since the latency of this reflex on the stimulated side in these 4 patients ranged from 35 to 42 ms with a mean of 39 ms, it is called here C reflex (Sutton and Mayer, 1974); that of the non-stimulated side is called C′ reflex. As shown in Table 3, the time difference between C and C′ was almost identical with the latency difference from the earlier positive peak of the contralateral SEP (N33 onset) to that of the ipsilateral SEP (N33′ onset) in 3 of the 4 patients.

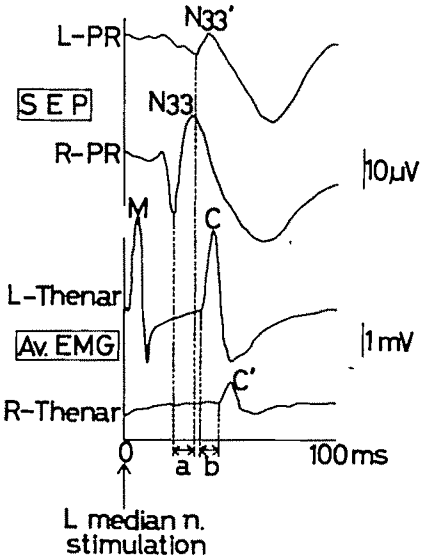


FIG. 4. SEP and C reflex in a 57-year-old female with progressive myoclonic epilepsy. Time difference from the C reflex onset to that of the non-stimulated side (C′) was 11 ms (b) and latency difference from the early positive peak of the contralateral high amplitude SEP to that of the ipsilateral SEP was 12 ms (a) M indicates M wave which was evoked directly in the thenar muscle by electrical stimulation of the median nerve. PR indicates the hand sensory area of the parietal cortex. L = left. R = right.

TABLE 3. LATENCY RELATIONSHIP BETWEEN THE ONSET OF THE C REFLEX AND THE EARLY POSITIVE PEAK PRECEDING THE N33 OF SEP IN 4 PATIENTS WITH PROGRESSIVE MYOCLONIC EPILEPSY (MS)

Case	*N33*	*C*	*N33′*	*C′*	*N33-N33′*	*C-C′*
KS	22	35	34	46	12	11
MK	27	40	42	49	15	9
YO	22	38	30	47	8	9
KO	28	42	37	51	9	9

N33′ = N33 recorded from the cerebral hemisphere ipsilateral to the stimulus. C′ = C reflex recorded from the thenar muscle of the non-stimulated side.

(6) *Relationship between the Myoclonus-related Spike and the High Amplitude SEP*

Of 7 patients with progressive myoclonic epilepsy, who were shown to have the myoclonus-related spike by the jerk-locked averaging technique, 6 patients showed a high amplitude SEP in response to electrical stimulation of the median nerve. The myoclonus-related spike and the high amplitude SEP in these patients were compared in terms of wave form, time relationship and topography.

First, the wave form of the myoclonus-related spike demonstrated by the jerk-locked averaging technique closely resembled that of the N33 of the high amplitude SEP (fig. 5), especially when the former was preceded by a positive sharp potential and followed by a large negative slow wave.

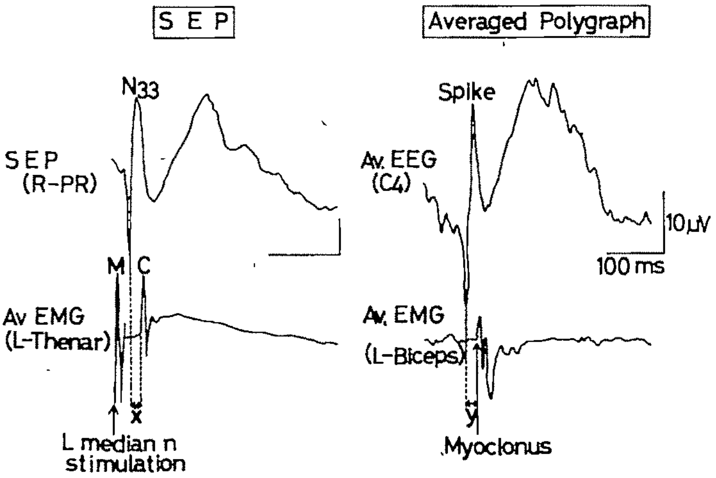


FIG. 5 SEP and polygraph obtained by jerk-locked averaging in a 17-year-old male with progressive myoclonic epilepsy. The wave form of the N33 component of the high amplitude SEP and that of the myoclonus-related spike resemble each other quite well Moreover, the time interval from the early positive peak of the SEP to the C reflex was 14 ms (x) and that from the onset of the cortical spike to the myoclonic discharge was 12 ms (y).

Comparison of the time interval from the onset of the cortical spike to the onset of the myoclonic jerk with that from the earlier positive peak preceding the N33 of the high amplitude SEP to the onset of the C reflex is shown in Table 4. The interval from spike to myoclonus was almost identical to or slightly shorter than that from the N33 to C reflex in each case examined.

Distribution of the myoclonus-related spike and that of the high amplitude SEP were compared in 3 subjects. The N33 component of the high amplitude SEP showed a phase reversal at the area corresponding to the contralateral precentral hand area, whereas the N20 component showed a phase reversal at the area corresponding to the post-central hand area as in the normal SEP. The myoclonus-related spike also showed a phase reversal at the contralateral central or precentral area (fig. 6).

Table 4. Comparison between the Time Interval from the Onset of the Myoclonus-related Cortical Spike to the Onset of the Myoclonic Jerk and that from the Early Positive Peak Preceding the N33 of the High Amplitude SEP to the Onset of the C Reflex in Patients with Progressive Myoclonic Epilepsy

Case	*Spike-Myoclonus* (*ms*)		*N33-C* (*ms*)
KS	Dorsal interossei	12	13
	Biceps	7	
KO	Flex. carpi ulnar.	14	14
KK	Brachioradialis	15	16
	Ext. indicis	10	
HK	Flex. carpi ulnar.	13	14
	Biceps	9-12	
KT	Brachioradialis	9	9
HY	Biceps	8-12	—
KH	Deltoid	7-14	—
YN		—	19
YO		—	17
MK		—	13

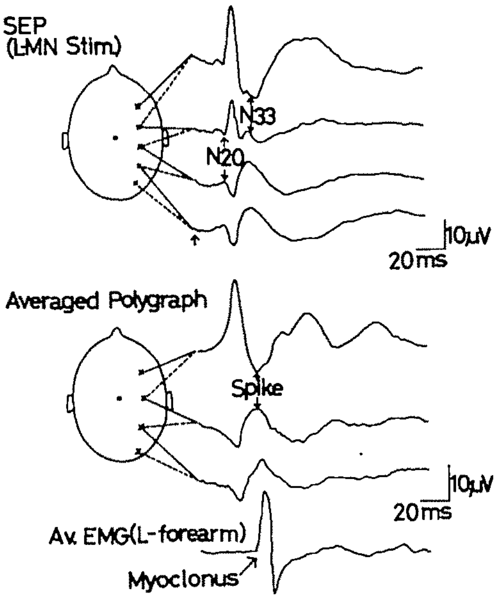


Fig. 6. Anteroposterior distribution of the N33 component of the high amplitude SEP and the myoclonus-related spike in a 19-year-old male with progressive myoclonic epilepsy. Both potentials are localized to the same area, corresponding to the precentral or central region. On the transverse derivations, both potentials showed a phase reversal at the contralateral central area.

DISCUSSION

The usefulness of the technique of jerk-locked averaging in studying myoclonus, which was first reported by the authors in 1975 (Shibasaki and Kuroiwa, 1975), was confirmed on a larger number of cases in the present study. The technique enabled us to visualize a cortical spike preceding the myoclonus in patients with progressive myoclonic epilepsy, when the conventional polygraph did not show any spike-and-wave complex in association with myoclonus. This fact seems to be quite significant, because the same might hold true for other convulsive disorders as well. Although, in some patients with progressive myoclonic epilepsy, spike-and-wave complexes were seen in occasional temporal relationship with the myoclonus by the conventional polygraphic technique, the temporal relationship between the two phenomena was often difficult to evaluate, and was, above all, very variable. The present averaging technique made it easier to study these cases. Since, even by this technique, the myoclonus-related cortical spike was detected exclusively in cases with progressive myoclonic epilepsy, this finding is important diagnostically as well.

The only difficulties met with in using this technique were in cases with infrequent myoclonus or those with very vigorous myoclonus. In either situation, it is quite difficult to obtain adequate averaging. Because of the infrequency of the myoclonus, the averaging technique could not be applied to the patients with 'epilepsy with myoclonus', and to some patients with Ramsay Hunt syndrome in the present series.

An extremely high amplitude SEP was found in the majority of patients with progressive myoclonic epilepsy, but in none of patients belonging to other groups in the present series. The result is in conformity with that of Halliday and Halliday (1970). Recognition of this abnormal SEP, therefore, seems to be quite important for the diagnosis and classification of myoclonus. Taking into account the result of the jerk-locked averaging, progressive myoclonic epilepsy seems to be characterized by two remarkable neurophysiological findings, an unusually large response to electrical stimulation of the peripheral nerve on one hand, and an association of the spontaneously occurring myoclonus with cortical spikes on the other.

In this regard, we were greatly impressed by a close similarity of certain parameters between the initial component of the high amplitude SEP and the myoclonus-related cortical spike detected by the present averaging technique. First of all, the wave form of the myoclonus-related spike was strikingly similar to that of the high amplitude SEP, especially when the former was followed by a high amplitude, negative slow wave. The amplitude of the N33 component of the high amplitude SEP was about three times greater than that of the myoclonus-related spike, but their durations were quite similar (36 ms for the SEP and 32 ms for the spike). It is particularly noteworthy that the time interval from the onset of the cortical spike to the onset of the corresponding myoclonic discharge was similar to, or slightly shorter than, that from the earlier positive peak preceding the N33 of the high amplitude SEP to the onset of the C reflex. Since C reflex was always recorded from a thenar muscle whereas myoclonic discharge was recorded from a more proximal muscle, these two time intervals are considered to be almost identical. As to the topographical distribution, both potentials were shown to occur predominantly over the contralateral hemisphere in all cases. Although a more precise study will be necessary in this regard, the present results, based on a small number of cases, indicated a close proximity of the scalp localization of these two potentials. They showed a phase reversal at the region corresponding to the precentral area contralateral to the stimulation or to the myoclonus.

It is postulated, from these facts, that the N33 component of the high amplitude SEP and the myoclonus-related cortical spike seen in patients with progressive myoclonic epilepsy might have a common physiological basis. This theory is of particular interest from the viewpoint of 'reflex' myoclonus (Halliday, 1967*b*; Pagni, Marossero, Cabrini, Ettorre and Infuso, 1971; Sutton and Mayer, 1974), because the cortical spike time-locked to the spontaneously occurring myoclonus could be in fact elicited by some inapparent stimulus.

In a study of a patient with 'focal reflex' myoclonus, Sutton and Mayer (1974) demonstrated an exaggerated response in the thenar muscle 48 to 54 ms (mean 51) following an electrical stimulus to the median nerve, and interpreted it as a cortical (C) reflex. In 3 out of 4 patients of the present series with progressive myoclonic epilepsy, the time difference between the C reflex of the stimulated side and that of the non-stimulated side was similar to the latency difference between the N33 of the contralateral SEP and that of the ipsilateral SEP. Taking into account the current theory that the early components of the SEP ipsilateral to the stimulus are conducted via the corpus callosum from the contralateral sensory cortex (Liberson, 1966; Eidelberg and Jenkins, 1966; Williamson, Goff and Allison, 1970; Tamura, 1972), the present finding seems to be in favour of the hypothesis that the cerebral cortex is participating in the C reflex loop.

The origin of myoclonus has long been a subject of controversy. Studies in this field centred on the time interval between the cortical spike and its associated myoclonic jerk. A shorter time interval than expected for the conduction of impulses from the motor cortex to the muscle was taken as one of the evidences to suggest the presence of a discharging focus in the deep cerebral structures (Dawson, 1946; Van Bogaert, Radermecker and Titeca, 1950; Bradshaw, 1954; Harriman and Millar, 1955; Lance and Adams, 1963; Kuroiwa, Ohta, Kato and Inoue, 1968; Shibasaki and Kuroiwa, 1975). The present study in 7 patients with progressive myoclonic epilepsy, who showed the myoclonus-related cortical spike by the jerk-locked averaging technique, demonstrated that the time interval was similar to that between the N33 component of the high amplitude SEP and the C reflex. It is postulated, therefore, that the myoclonus in these patients could be of cortical origin and conducted via the corticospinal tract. In this sense, myoclonus of this type corresponds to the 'pyramidal' type of Halliday's classification (Halliday, 1967*a*, *b*), or what Hallett, Chadwick, Adam and Marsden (1977) call 'cortical loop reflex' type. The conduction of impulses from the internal capsule to the biceps brachii and to the dorsal interossei muscles of the contralateral upper extremity in man is known to take 9 to 15 ms and 19 to 20 ms, respectively (Pagni, Ettorre, Infuso and Marossero, 1964). The time interval of 7 to 15 ms in the present series of patients with progressive myoclonic epilepsy seems to be compatible with the above conduction time, particularly when the shorter stature of the Japanese is taken into consideration.

SUMMARY

Electroencephalographic studies were carried out in 30 patients with various kinds of myoclonus. It was confirmed that the technique of jerk-locked averaging with a backward averaging program was useful for detecting cortical spikes in association with the spontaneously occurring myoclonus, which are not recognized on the conventional polygraph, and for evaluating the temporal and topographical relationship between the spike and the myoclonus. By this technique, cortical spikes were shown to precede the myoclonus of a contralateral upper extremity muscle by 7 to 15 ms in all patients with progressive myoclonic epilepsy, but in none of the patients with other types of myoclonus.

The majority of patients with progressive myoclonic epilepsy showed a high amplitude somatosensory evoked potential (SEP) in response to electrical stimulation of the median nerve. The N33 component of this high amplitude SEP was found to be similar to the myoclonus-related cortical spike in their wave form, time relationship and topographical distribution, suggesting an involvement of similar physiological mechanisms in the genesis of both phenomena. Myoclonus in these patients is compatible with 'pyramidal' or 'cortical loop reflex' type.

Postscript

After this paper was submitted, the paper by Chadwick, D., Hallett, M., Harris, R., Jenner, P., Reynolds, E. H. and Marsden, C. D. (1977), Clinical, biochemical and physiological features distinguishing myoclonus responsive to 5-hydroxytryptophan, tryptophan with a monoamine oxidase inhibitor, and clonazepam, *Brain*, **100**, 455–487, came to our attention, in which they reported similar EEG-EMG correlations on the polygraph in some patients with post-anoxic myoclonus, a type which we have not yet been able to study.

ACKNOWLEDGEMENTS

This paper was read at the 9th International Congress of Electroencephalography and Clinical Neurophysiology in Amsterdam on September 11, 1977. The authors are very grateful to Dr. A. M. Halliday, of the National Hospital for Nervous Diseases, Queen Square, London, for his kind revision of this article and for his valuable advice.

REFERENCES

BRADSHAW, J. P. P. (1954) A study of myoclonus. *Brain*, **77**, 138–157.

DAWSON, G. D. (1946) The relation between the electroencephalogram and muscle action potentials in certain convulsive states. *Journal of Neurology, Neurosurgery and Psychiatry*, **9**, 5–22.

—— (1947) Investigations on a patient subject to myoclonic seizures after sensory stimulation. *Journal of Neurology, Neurosurgery and Psychiatry*, **10**, 141–162.

EIDELBERG, E. and JENKINS, I. (1966) Organization of somatic sensory mechanisms in the *macaque* cerebral cortex. *Electroencephalography and Clinical Neurophysiology*, **21**, 452–460.

ENGEL, J., JR., RAPIN, I. and GIBLIN, D. R. (1977) Electrophysiological studies in two patients with cherry red spot-myoclonus syndrome. *Epilepsia*, **18**, 73–87.

GASTAUT, H. and RÉMOND, A. (1952) Étude électroencéphalographique des myoclonies. *Revue Neurologique*, **86**, 596–609.

GRINKER, R. R., SEROTA, H. and STEIN, S. I. (1938) Myoclonic epilepsy. *Archives of Neurology and Psychiatry, Chicago*, **40**, 968–980.

HAGUENAU, J., CHRISTOPHE, J., RÉMOND, A. and PECKER, J. (1950) Epilepsie myoclonique progressive généralisée. Etude clinique et bioélectrique. *Revue Neurologique*, **82**, 116–122.

HALLETT, M., CHADWICK, D., ADAM, J. and MARSDEN, C. D. (1977) Reticular reflex myoclonus: a physiological type of human post-hypoxic myoclonus. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 253–264.

HALLIDAY, A. M. (1967*a*) The clinical incidence of myoclonus. In: *Modern Trends in Neurology*, 4th Edition. Edited by D. Williams. London: Butterworths, pp. 69–105.

—— (1967*b*) The electrophysiological study of myoclonus in man. *Brain*, **90**, 241–284.

—— (1975) The neurophysiology of myoclonic jerking—a reappraisal. In: *Myoclonic Seizures*. Edited by M. H. Charlton. Amsterdam: Excerpta Medica, pp. 1–29.

—— and HALLIDAY, E. (1970) Cortical evoked potentials in patients with benign essential myoclonus and progressive myoclonic epilepsy. *Electroencephalography and Clinical Neurophysiology*, **29**, 106–107.

HAMBERT, O. and PETERSÉN, I. (1970) Clinical, electroencephalographical and neuropharmacological studies in syndromes of progressive myoclonus epilepsy. *Acta Neurologica Scandinavica*, **46**, 149–186.

HARRIMAN, D. G. F. and MILLAR, J. H. D. (1955) Progressive familial myoclonic epilepsy in three families: its clinical features and pathological bases. *Brain*, **78**, 325–349.

KUROIWA, Y., OHTA, M., KATO, M. and INOUE, N. (1968) Time interval between cortical spike and muscle discharge in patients with myoclonus (in Japanese). *Clinical Electroencephalography, Osaka*, **10**, 24–28.

LANCE, J. W. and ADAMS, R. D. (1963) The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain*, **86**, 111–136.

LIBERSON, W. T. (1966) Study of evoked potentials in aphasics. *American Journal of Physical Medicine*, **45**, 135–142.

PAGNI, C. A., ETTORRE, G., INFUSO, L. and MAROSSERO, F. (1964) EMG responses to capsular stimulation in the human. *Experientia*, **20**, 691-692.

—— MAROSSERO, F., CABRINI, G., ETTORRE, G. and INFUSO, L. (1971) Physiopathology of stimulus sensitive myoclonus: a stereo-EEG study. *Electroencephalography and Clinical Neurophysiology*, **31**, 176.

ROSÉN, I., FEHLING, C., SEDGWICK, M. and ELMQVIST, D. (1977) Focal reflex epilepsy with myoclonus: electrophysiological investigation and therapeutic implications *Electroencephalography and Clinical Neurophysiology*, **42**, 95-106.

SHIBASAKI, H., KATO, M. and KUROIWA, Y. (1973) Essential myoclonus with paroxysmal EEG activity. Report of a case and electrophysiological study (in Japanese). *Clinical Neurology, Tokyo*, **13**, 203-210.

—— and KUROIWA, Y. (1975) Electroencephalographic correlates of myoclonus. *Electroencephalography and Clinical Neurophysiology*, **39**, 455-463.

—— LOGOTHETIS, J. A. and TORRES, F. (1971) Intention myoclonus: A case report. *Neurology, Minneapolis*, **21**, 655-658.

—— YAMASHITA, Y. and TSUJI, S. (1977) Somatosensory evoked potentials. Diagnostic criteria and abnormalities in cerebral lesions. *Journal of the Neurological Sciences*, **34**, 427-439.

SUTTON, G. G. (1975) Receptors in focal reflex myoclonus. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 505-507.

—— and MAYER, R. F. (1974) Focal reflex myoclonus. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 207-217.

TAMURA, K. (1972) Ipsilateral somatosensory evoked responses in man. *Folia Psychiatrica et Neurologica Japonica*, **26**, 83-94.

VAN BOGAERT, L., RADERMECKER, J. and TITECA, J. (1950) Les syndromes myocloniques. *Folia Psychiatrica Neurologica et Neurochirurgica Neerlandica*, **53**, 650-690.

WATSON, C. W. and DENNY-BROWN, D. (1955) Studies of the mechanism of stimulus-sensitive myoclonus in man. *Electroencephalography and Clinical Neurophysiology*, **7**, 341-356.

WILLIAMSON, P D., GOFF, W. R. and ALLISON, T. (1970) Somato-sensory evoked responses in patients with unilateral cerebral lesions. *Electroencephalography and Clinical Neurophysiology*, **28**, 566-575.

(*Received January 5, 1978*)

Bram (1978), **101**, 461–472

FAMILIAL MYOCLONIC EPILEPSY WITH ATAXIA AND NEUROPATHY WITH ADDITIONAL FEATURES OF FRIEDREICH'S ATAXIA AND PERONEAL MUSCULAR ATROPHY

by N. J. SMITH, M. L. E. ESPIR *and* W. B. MATTHEWS

(*From the Department of Neurology, Derbyshire Royal Infirmary, Derby DE1 2QY*)

INTRODUCTION

AMONG the hereditary diseases of the nervous system, it is well recognized that certain conditions frequently occur together within particular families. Progressive myoclonic epilepsy is often associated with ataxia (Halliday, 1967), and myoclonic epilepsy sometimes occurs in cases of Friedreich's ataxia (Hunt, 1921). Many individuals and families have been reported with both Friedreich's ataxia and peroneal muscular atrophy (Charcot-Marie-Tooth disease) (Roth, 1948). Neither the association of myoclonic epilepsy with peroneal muscular atrophy, nor the occurrence of both conditions in a family in which there is also hereditary ataxia, appears to have been reported previously. We report here such a family (fig. 1), in which four members were affected. One had all three conditions and another had additional features of Friedreich's ataxia.

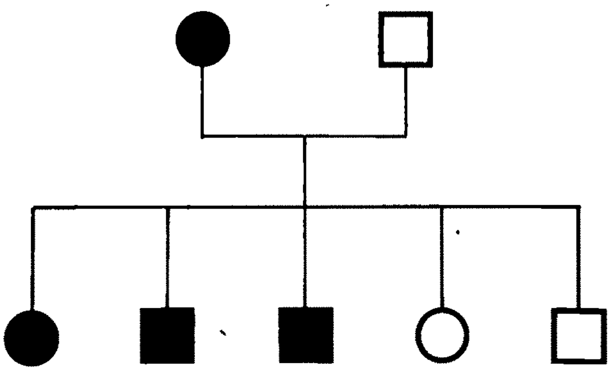


FIG. 1 Family tree, showing affected members (● ■).

PATIENTS

Case histories are summarized in Table 1.

Patient I.1

This patient, born in 1932, was the third daughter of parents who were not known to be related. Her parents were not available for examination, but she stated that they had no neurological disorder. Her five siblings were similarly said to be unaffected.

Early development was normal. At the age of 23 years she began to have myoclonic jerks on rising each morning. The myoclonus lasted for about one minute, and was not associated with loss of consciousness. In spite of treatment with phenobarbitone, and later pheneturide, she continued to have myoclonus in the mornings. Ten years later, the myoclonic jerks were accompanied by momentary loss of consciousness and myoclonus would recur later in the day if she missed a dose of anticonvulsant. During the last two years she has had treatment with clonazepam 1·5 mg daily, but the myoclonus has continued.

When examined again at the age of 44 in 1976, she could not run or walk heel-to-toe, and there was ataxia in all four limbs, more marked on the right. She had mild dysarthria, but no nystagmus. Vibration sense was lost below the knees, but joint position sense was retained. There was no wasting or weakness; tendon reflexes were normal, and plantar responses were flexor.

Her electro-encephalogram (EEG) showed a generalized excess of theta activity with frequent bursts of symmetrical slow activity (3–4 Hz), and multiple spikes. These paroxysms occurred spontaneously, but could also be precipitated by closing the eyes, and by photic stimulation (fig. 2).

Electromyography and nerve conduction studies showed no abnormality.

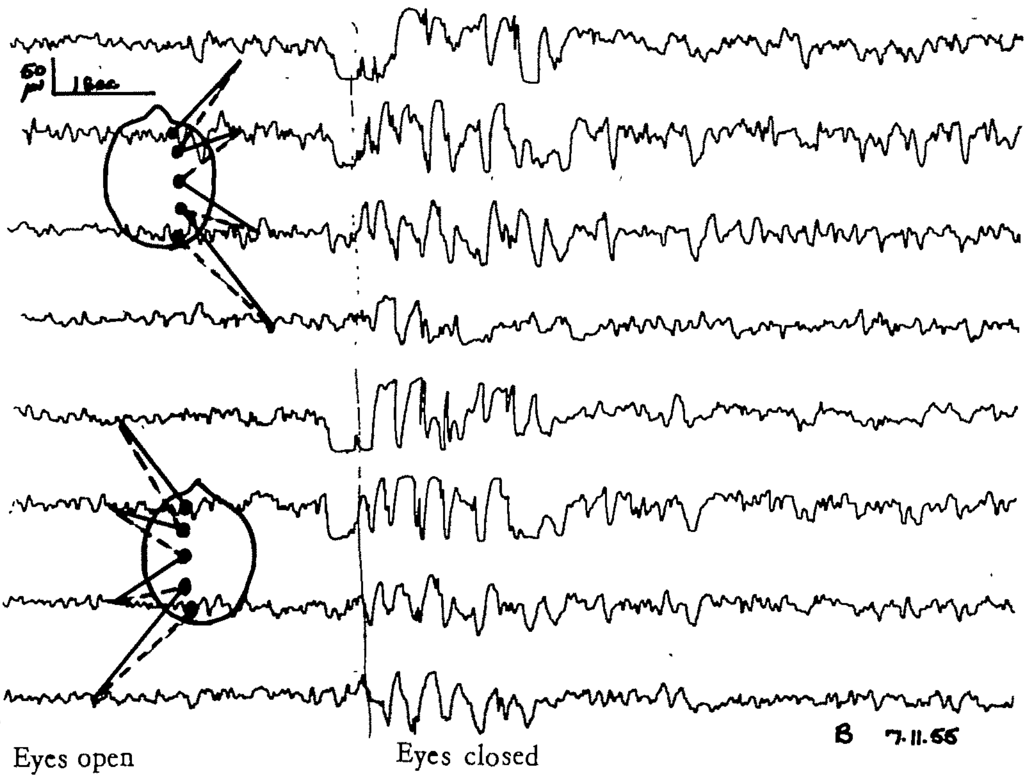


Fig 2. EEG of Patient I.1.

Patient II.1

This girl, born in 1951, was mentally backward, and attended a special school for educationally subnormal children. At the age of 11 years her IQ was recorded as 68, but physical examination was normal. When aged 13 she developed unsteadiness of gait, with frequent falls. One year later examination showed bilateral foot-drop, with slight wasting of the anterior tibial muscles bilaterally, and of the thenar eminence of the right hand. There was generalized areflexia, with pes cavus. There was no scoliosis, ataxia or sensory impairment, the plantar responses were flexor. At the age of 15½ the muscle wasting was more marked, and vibration sense had been lost in the legs.

She worked in a woollen mill after leaving school, but had to give up work after a few years because of progressive weakness and unsteadiness. In 1975, at the age of 24, she developed occasional myoclonic jerks, occurring in the early morning and late at night. She became depressed, and was admitted to hospital on several occasions after taking overdoses of drugs.

When seen again in September 1976 she had marked dysarthria, with nystagmus on lateral gaze to both sides. There was marked ataxia with gross distal wasting (*see* fig. 3) and absent tendon reflexes in all limbs. The plantar responses were flexor. Vibration sense was absent in the legs, but joint position sense was intact.

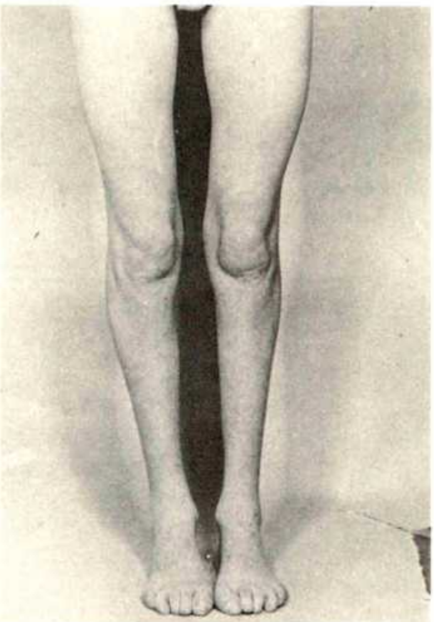


FIG. 3. Wasting in the legs of Patient II.1.

Her EEG in 1975 (fig. 4) showed frequent bursts of rhythmic 3 Hz slow waves bilaterally, with occasional isolated low voltage spikes. Later records showed variable amounts of high voltage slow activity, without spikes. During an episode of myoclonus a surface electrode on the arm did not show any correlation between the jerks and paroxysmal activity in the EEG.

The nerves in her legs could not be stimulated electrically. In the arms motor and sensory nerve conduction velocities were normal or only slightly reduced, but there was marked reduction of amplitude of sensory action potentials. There were denervation changes in the electromyogram (Table 2).

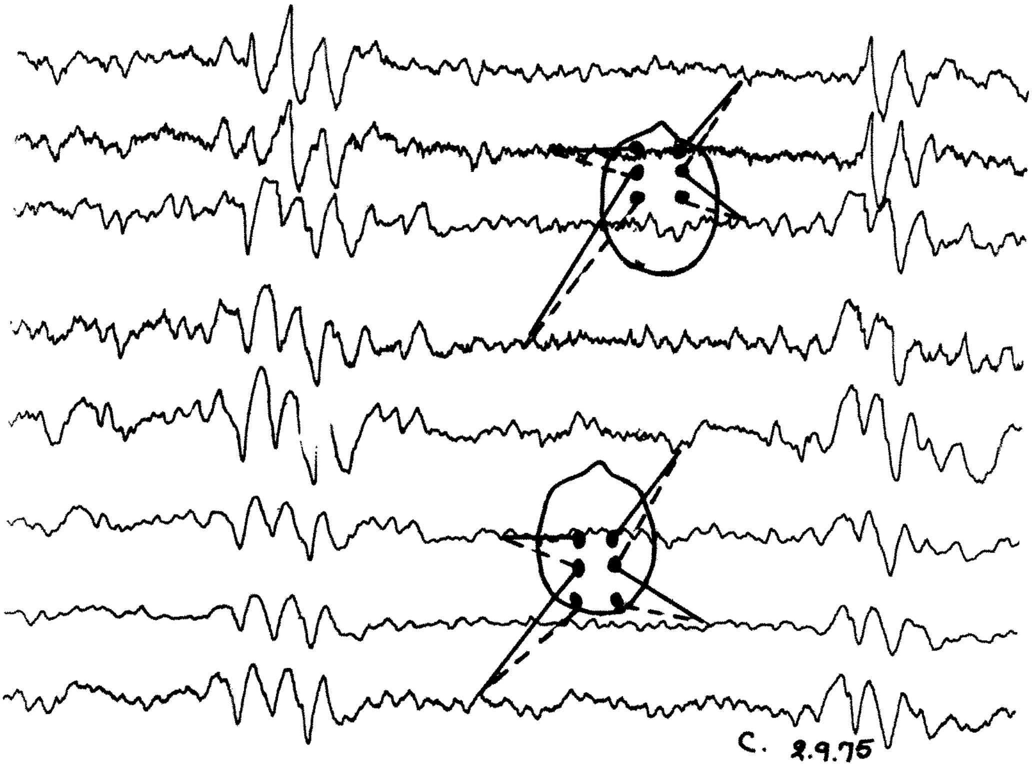


FIG. 4. EEG of Patient II.1.

Patient II.2

This boy, born in 1953, was noted to have nocturnal myoclonus in childhood. Early development was normal, and physical examination at the age of 13 years showed no abnormality.

In 1970, at the age of 18, he developed myoclonic jerks in the early mornings. The jerks affected the arms predominantly, and the legs occasionally; there was no loss of consciousness. During the next few years he developed progressive unsteadiness of gait, with clumsiness of the arms, causing him to give up work at the age of 21.

He was examined again in September 1976. Myoclonus was occasionally present, with asterixis and marked ataxia in all four limbs. There was moderate dysarthria, with nystagmus on lateral gaze to both sides. Vibration sense was absent in the legs, but joint position sense was intact. There was no wasting or weakness, all tendon reflexes were present, and the plantar responses were flexor.

His EEG (fig. 5) showed a slow background (4 Hz), with bursts of high voltage delta activity and occasional bilateral spikes. The paroxysmal activity was produced by flicker at speeds between 6 and 17 Hz and by eye closure.

There was moderate delay in motor nerve conduction velocities in both legs. EMG showed a reduced interference pattern and myoclonic discharges in all muscles sampled in both arms and legs (*see* Table 2).

Patient II.3

This boy was born in 1954 and when 6 years old it was noticed that he was unsteady on his feet. He had frequent falls but the only abnormal physical signs were a slight degree of intention tremor and past-pointing and unsteadiness on rising from a chair. Within one year he required occasional help to

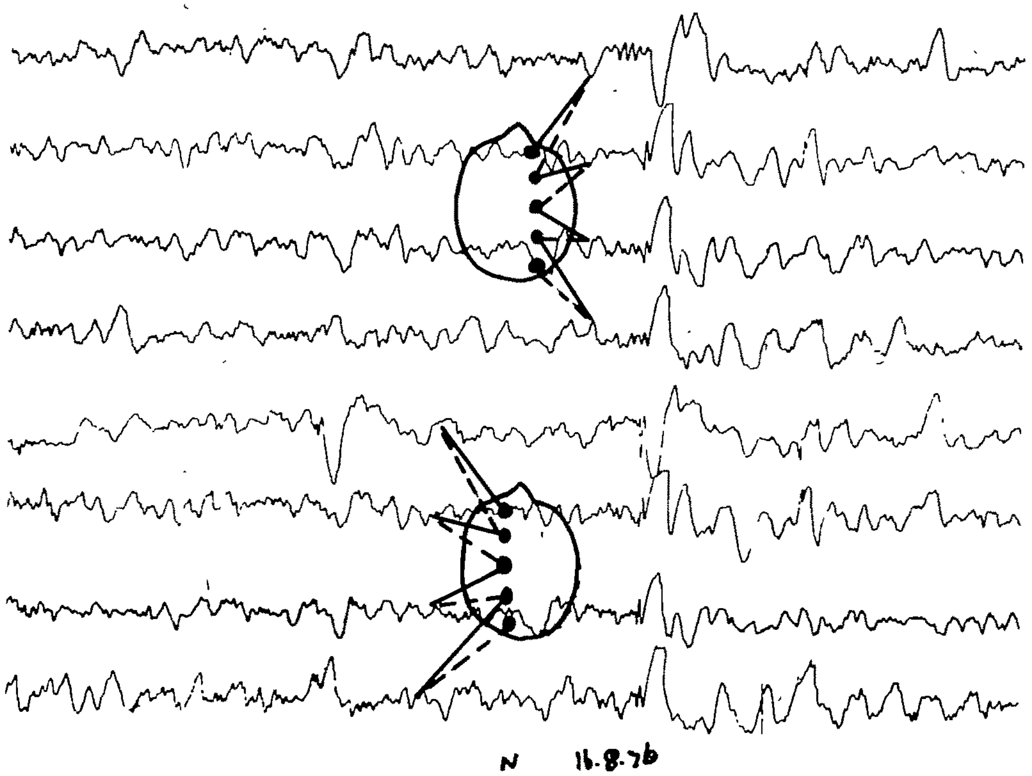


FIG. 5. EEG of Patient II.2

feed himself, but was still able to run, although he often fell. Examination in 1960 showed bilateral pes cavus, marked ataxia of all limbs, and extensor plantar responses. Power, reflexes and all modalities of sensation were normal.

Investigation in 1962 showed widespread T-wave inversion in the ECG. The urine contained no excess of porphyrins, chromatography was normal, and no metachromatic granules were detected. The CSF was normal, and the WR was negative in both serum and CSF.

His unsteadiness increased over the next few years, and he became dysarthric. In 1965, at the age of 11, he had nystagmus, the tendon reflexes had been lost, and the plantar responses were extensor. Vibration sense was absent in the legs, and the previously noted ataxia was more marked.

During the next ten years he had occasional grand mal convulsions, and developed frequent myoclonic jerks. He was increasingly disabled by the ataxia.

Examination in March 1975 showed bilateral optic atrophy, with impaired conjugate deviation of the eyes to right more than left, and coarse nystagmus. There were diffuse myoclonic jerks, with generalized weakness and wasting, so that he could not lift his legs off the bed. His speech was almost unintelligible.

His EEG (fig. 6) had a slow background (4–6 Hz). There were frequent bilateral delta wave discharges, at times almost continuous, and isolated spikes occurred occasionally. Myoclonic jerks were associated with some of the spike discharges. Photic stimulation produced further delta wave discharges with occasional spikes.

Electromyography and nerve conduction studies were not performed.

In June 1975, at the age of 21, he developed bronchopneumonia after a series of fits. He died at another hospital, and no post-mortem examination was performed.

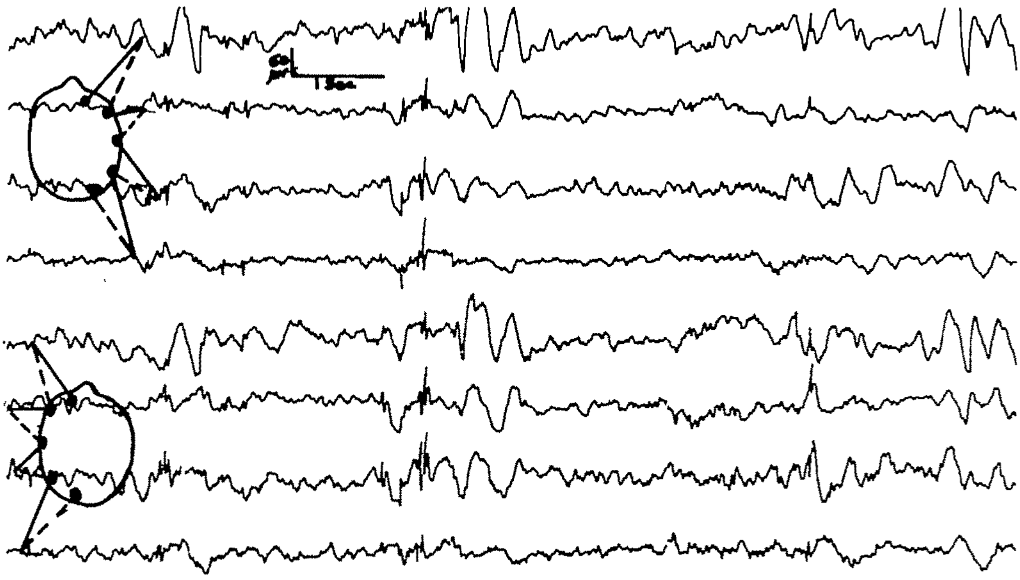


FIG. 6. EEG of Patient II.3

TABLE 1 SUMMARY OF CLINICAL FEATURES OF AFFECTED MEMBERS

	I.1	*II.1*	*II.2*	*II.3*
Intellect	Normal (44)	Low (11)	Normal (23)	Normal (21)
Myoclonus	+ (23)	+ (25)	+ (18)	+ (15)
Convulsions	+ (33)	− (25)	− (23)	+ (12)
Optic atrophy	− (44)	− (25)	− (23)	+ (20)
Ataxia	+ (44)	+ (25)	+ (21)	++ (6)
Weakness and wasting	− (44)	++ (13)	− (23)	+ (20)
Reflexes	Normal (44)	Absent (14)	Normal (23)	Absent (11)
Plantar responses	Flexor (44)	Flexor (25)	Flexor (23)	Extensor (7)
Joint sense	Present (44)	Present (25)	Present (23)	Present (16)
Vibration sense	Absent (44)	Absent (14)	Absent (23)	Absent (11)
Pes cavus	− (44)	+ (13)	− (23)	+ (6)
Disability	+ (44)	+++ (20)	++ (21)	+++ (16) Died aged 21 yrs

Figures in brackets indicate the earliest age at which the abnormality was detected, or the latest age of the normal finding.

Siblings II.4 and II.5

The two remaining siblings were born in 1956 and 1961. They were both of normal intelligence and had no history of fits or myoclonus. Physical examination, EEG, EMG and nerve conduction studies were normal in September 1976.

TABLE 2. NERVE CONDUCTION AND ELECTROMYOGRAPHIC STUDIES

Patient	*Nerve*	*Conduction velocity (m/s)*	*Terminal latency (ms)*	*EMG*
I.1	R. lat. pop.	40	5·7	Normal interference pattern
	R. post. tib.	39	5·8	
II.1	Leg nerves could not be stimulated			Reduced interference pattern. Single, high amplitude polyphasic units
	R. median (motor)	47	4·2	
	L. median "	47	3·9	
	R. ulnar "	53	2·9	
	L. ulnar "	38	3·0	
	L. ulnar (sensory)	56	2·8	
II.2	R. lat. pop.	31	6·4	Reduced interference pattern. Myoclonic discharges in all muscles at rest.
	L. lat. pop.	40	6·5	
	R. median (motor)	53		
	(sensory antidromic)	47	2·8	
	R. ulnar	55	3·0	
II.3	Studies not performed.			
II.4	R. lat. pop.	47	4·2	Normal interference pattern.
	R. post. tib.	49	4·2	
II.5	R. lat. pop.	48	3·4	Normal interference pattern.
	R. post. tib.	48	4·4	

METABOLIC INVESTIGATIONS

Fasting blood glucose and 90 min post-prandial blood glucose concentrations were normal in all affected members. Fasting serum cholesterol and lipoprotein electrophoresis were normal in patients I.1 and II.1. Urinary amino acid electrophoresis was normal in all affected members, and the cetyl tri-methyl ammonium test (CTAB) was negative in Patients I.1, II.1 and II.2. Other members of the family were not studied. There was no excess of indican in the urine of Patients I.1 and II.1.

DISCUSSION

The family described here shows myoclonic epilepsy with associated neurological disorders in a woman and three of her five children. There was no evidence of a lipidosis or other metabolic disorder. Patients I.1 and II.1 had moderate ataxia in addition to myoclonic epilepsy. Each also had loss of vibration sense in both legs, but no other evidence of neuropathy. Patient II.1 had a similar degree of ataxia, but with gross distal wasting and weakness in all four limbs. Her legs were more severely affected than the arms, and the nerves in her legs could not be stimulated electrically. In the arms there were electrical changes consistent with the neuronal form of peroneal muscular atrophy (Buchthal and Behse, 1977). Patient II.3 also developed myoclonic epilepsy in association with the clinical features of Friedreich's ataxia (progressive ataxia beginning in the legs, dysarthria, weakness, areflexia, loss of vibration sense, extensor plantar responses and electrocardiographic evidence of a cardiomyopathy) (Barbeau, 1976).

In previously reported families with progressive myoclonic epilepsy, metabolic studies have shown an abnormally low serum mucoprotein level (Millar and Neill, 1959; Tukel and Çaliskan, 1954) although no such abnormality was found in the family described by Matthews, Howell and Stevens (1969), nor in any of our patients. High urinary levels of an acid mucopolysaccharide (Poulsen, 1975) and of indican (Koskiniemi, 1975) have also been observed in some families, but were not present in our patients.

In the absence of pathological evidence, it is assumed that the affected members of this family show the variable clinical manifestations of a single genetic disorder, rather than the chance coincidence of unrelated conditions. Inheritance in this family appears to be autosomal dominant, the affected mother passing on the condition to three of her five children, regardless of their sex. Patient I.1 stated that as far as she knew, none of her ancestors was affected but no member of the previous generation was examined. There is therefore a possibility of a spontaneous mutation being responsible for the abnormality which first appeared in Patient I.1.

Patient I.1 was not aware of any consanguinity in her ancestors. Consanguinity, however, is common in families with progressive myoclonic epilepsy (Matthews, Howell and Stevens, 1969) and in families showing the association of Freidreich's ataxia and peroneal muscular atrophy (Becker, 1966); the inheritance is then assumed to be autosomal recessive. However, dominant inheritance has been observed in both types of family (Becker, 1966; Diebold, 1972), but rapid progression and early death is then unusual.

If the members of this family are arranged in descending order of the severity of their disability (II.3, II.1, II.2, I.1), the corresponding ages of onset are 6, 13, 18 and 23 years respectively. The severity of the disease in this family is, therefore, related inversely to the age of onset. There is theoretical justification for regarding the age of onset as a manifestation of the severity of an hereditary condition (Haldane, 1941), and Koskiniemi, Donner, Majuri, Haltia and Norio (1974) have found a similar relation between prognosis and age of onset in 93 Finnish cases of progressive myoclonic epilepsy. In the family described here the two unaffected members of the second generation are now aged only 15 and 20 years respectively; it is possible that they may develop a mild form of the familial disease in later life.

In the family described here the eldest member of the second generation has peroneal muscular atrophy, while a younger member has Friedreich's ataxia. A similar relationship between birth order and manifestations was seen in the family described by Popow (1932), and in two generations of the family described by Spillane (1940).

Ataxia in Progressive Myoclonic Epilepsy

Progressive myoclonic epilepsy is usually familial, but there are occasional isolated cases. There are three pathological types: (1) those suffering from a lipidosis, particularly a gangliosidosis, (2) those with intracellular deposits of mucopolysaccharide in the brain and other organs (Lafora bodies), (3) a group of cases showing degenerative changes in the cerebellum and cerebellar pathways; this last group has no pathological evidence of lipidosis or Lafora bodies.

Progressive ataxia with dementia and visual failure may occur in all three forms of the disease (Matthews, Howell and Stevens, 1969; Schwartz and Yanoff, 1965; Yamamoto, Adachi, Kawamura, Takahashi, Kitani, Ohtori, Shinji and Nishikawa, 1974), and there may be muscle wasting in the late stages. All affected members of the family described here had ataxia and dysarthria of variable severity, in addition to myoclonic epilepsy, and all except one (I.1) had nystagmus. The onset of the disease in Patient II.3 was at the age of 6 years; he developed the most severe ataxia, with additional features of Friedreich's ataxia, as described above, and he died at the age of 21. The association of myoclonic epilepsy with Friedreich's ataxia, as in this case, was first described by Hunt (1921), and later by Hodskins and Yakovlev (1930), Ziegler, Van Speybroech and Seitz (1974) and Skre (1975), and with a hereditary ataxia other than Friedreich's by Gilbert, McEntee and Glaser (1963) and Ekbom (1975). Noad and Lance (1960) described four children of a consanguineous marriage who had myoclonic epilepsy and ataxia; one of these cases had pes cavus, but there were no other signs of Friedreich's ataxia or peroneal muscular atrophy. Christophe and Gruner (1956) found pathological features of Friedreich's ataxia in a patient who had myoclonic epilepsy and ataxia, but no other features of Friedreich's ataxia during life. Friedreich's ataxia, however, has only been reported in families with the degenerative form of myoclonic epilepsy and not with a lipidosis or Lafora's disease. For these reasons Halliday (1967) stated that the presence of pes cavus, as in two members of the family described here (II.1 and II.3), indicates that the underlying pathology is of the degenerative type.

Friedreich's Ataxia and Peroneal Muscular Atrophy

The occurrence of Friedreich's ataxia and peroneal muscular atrophy (Charcot-Marie-Tooth) in members of the same family has been recognized since the early years of the twentieth century and this literature was reviewed by Roth (1948), Greenfield (1954) and Becker (1966). These families may be divided into two categories according to the clinical features and mode of inheritance.

The first category consists of families showing a relatively mild disorder, usually with autosomal dominant inheritance (Spillane, 1940; Hierons, 1956; Shepherd, 1955; and Gilbert, 1963). In these families some members showed features of Friedreich's ataxia, others had peroneal muscular atrophy, and others had an abortive form consisting only of pes cavus with absent tendon reflexes (Roussy and Lévy, 1926).

In the second category of families, Friedreich's ataxia and peroneal muscular atrophy occurred sporadically; individual members showing severe manifestations of one or both disease with a high incidence of parental consanguinity (Pappworth and O'Mahony, 1954; Becker, 1966; Tilbery, Altimari, Gagliardi-Fereira and Nieto, 1972). The inheritance in these families appears to have been autosomal recessive. German authors, regarding this form of the combination of Friedreich's ataxia and peroneal muscular atrophy as a separate entity, have called it 'Myatrophische Ataxia' (Conrad and Ott, 1955; Hopf and Port, 1968).

Other disorders may be associated; for example, Stephens, Hoover and Denst (1958) described a family with progressive supranuclear ophthalmoplegia in addition to ataxia and neuropathy in members of one generation, and an abortive form in two subsequent generations.

Skre and Lõken (1970) described three patients with Friedreich's ataxia and peroneal muscular atrophy, from two families, both with a history of consanguinity. These patients also developed myoclonus with convulsions, but only in the terminal stages. They had electroencephalographic and pathological evidence of a spongiform encephalopathy. These patients differed from the family we report in that the myoclonus and convulsions occurred only as a terminal event. None of the other families reported previously with Friedreich's ataxia and peroneal muscular atrophy have also had progressive myoclonic epilepsy.

Genetic and Clinical Synthesis

Roth (1948) suggested the presence of a subsidiary modifying gene to explain the variable clinical manifestations in families showing the combination of Friedreich's ataxia and peroneal muscular atrophy. Support for this view has been found by Thomas, Calne and Stewart (1974) in families with peroneal muscular atrophy. In the family described here, the variability in age of onset and clinical manifestations may be explained by the action of one or more subsidiary modifying genes. The terms 'peroneal muscular atrophy' and 'Friedreich's ataxia' may then be regarded as labels for particular combinations of clinical features, rather than as distinct genetic entities.

SUMMARY

A family is described in which a mother and three of her five children showed myoclonic epilepsy. The mother and one son were also ataxic; one other son had additional features of Friedreich's ataxia, and a daughter had peroneal muscular atrophy as well as myoclonic epilepsy and ataxia. Although some of these disorders have been associated in previously reported families, the occurrence of all three disorders in members of one family seems to be unique. It is concluded that this family shows the manifestations of one, probably dominant, gene. The differences in age of onset and manifestations may be explained by the action of one or more subsidiary genes.

ACKNOWLEDGEMENTS

We are grateful to Dr. Mari Simpson for the nerve conduction and electromyographic studies and to Dr. W. H. S. George for the metabolic studies.

REFERENCES

BARBEAU, A. (1976) Friedreich's Ataxia 1976—an overview. *Canadian Journal of Neurological Sciences*, **3**, 389-397.

BECKER, P. E. (1966) Krankheiten mit hauptsächlicher Beteiligung des spino-zerebellaren systems: Myatrophische Ataxie. In: *Humangenetik*. Edited by P. E. Becker. Stuttgart: Thieme Verlag, Vol. 5/1, pp. 226-230.

BUCHTHAL, F. and BEHSE, F. (1977) Peroneal muscular atrophy. *Brain*, **100**, 41-66.

CHRISTOPHE, J. and GRUNER, J. (1956) La dyssynergie cérébelleuse myoclonique de Ramsay Hunt. *Revue Neurologique*, **95**, 297-309.

CONRAD, K. and OTT, B. (1955) Ueber Beziehungen zwischen neuraler Muskelatrophie und hereditärer Ataxie (Friedreich). *Medizinische Klinik*, **50**, 638-640.

DIEBOLD, K. (1972) Vier Erbtypen oder Krankheitsformen der progressiven Myoklonusepilepsien. *Archiv für Psychiatrie und Nervenkrankheiten*, **215**, 362-375.

EKBOM, K. (1975) Hereditary ataxia, photomyoclonus, skeletal deformities and lipoma. *Acta Neurologica Scandinavica*, **51**, 393-404.

GILBERT, G. J. (1963) Familial ataxia with atrophy. *World Neurology*, **3**, 753-764.

—— MCENTEE, W. J. and GLASER, G. H. (1963) Familial myoclonus and ataxia. *Neurology, Minneapolis*, **13**, 365-372.

GREENFIELD, J. G. (1954) *The Spino-cerebellar Degenerations*. Oxford: Blackwell.

HALDANE, J. B. S. (1941) The relative importance of principal and modifying genes in determining some human diseases. *Journal of Genetics*, **41**, 149-157.

HALLIDAY, A. M. (1967) The clinical incidence of myoclonus. In: *Modern Trends in Neurology*. Edited by D. Williams. London: Butterworth, Vol. 4, pp. 69-105.

HIERONS, R. (1956) Familial peroneal muscular atrophy and its association with the familial ataxias and tremor and longevity. *Journal of Neurology, Neurosurgery and Psychiatry*, **19**, 155-160.

HODSKINS, M. B. and YAKOVLEV, P. I. (1930) Anatomico-clinical observations on myoclonus in epileptics and on related symptom complexes. *American Journal of Psychiatry*, **9**, 827-848.

HOPF, H C. and PORT, F. K. (1968) Friedreichsche Ataxie mit Beteiligung der peripheren Nerven nach Art der neuralen Muskelatrophie (Myatrophische Ataxie). *Deutsche Zeitschrift für Nervenheilkunde*, **194**, 1-16.

HUNT, J. R. (1921) Dyssynergia cerebellaris myoclonica—primary atrophy of the dentate system: a contribution to the pathology and symptomatology of the cerebellum. *Brain*, **44**, 490-537.

KOSKINIEMI, M. (1975) Findings in routine laboratory examination in progressive myoclonus epilepsy. *Acta Neurologica Scandinavica*, **51**, 12-20.

—— DONNER, M., MAJURI, H., HALTIA, M. and NORIO, R. (1974) Progressive myoclonus epilepsy. *Acta Neurologica Scandinavica*, **50**, 307-332.

MATTHEWS, W. B., HOWELL, D. A. and STEVENS, D. L. (1969) Progressive myoclonus epilepsy without Lafora bodies. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 116-122.

MILLAR, J. H. D. and NEILL, D. W. (1959) Serum mucoproteins in progressive familial myoclonic epilepsy (a preliminary note). *Epilepsia*, **1**, 115-116.

NOAD, K. B. and LANCE, J. W. (1960) Familial myoclonic epilepsy and its association with cerebellar disturbance. *Brain*, **83**, 618-630.

PAPPWORTH, M. H. and O'MAHONY, P. F. (1954) An unusual familial cerebellar syndrome. *Journal of Nervous and Mental Diseases*, **119**, 437-440.

POPOW, A. (1932) Une famille atteinte d'une forme particulière de maladie héréditaire. (Forme de Roussy-Lévy). *Revue Neurologique*, **2**, 447-462.

POULSEN, J. H. (1975) The excretion patterns of urinary glucosaminoglycans in a family with progressive familial myoclonus epilepsy. *Acta Neurologica Scandinavica*, **52**, 216-230.

ROTH, M. (1948) On a possible relationship between hereditary ataxia and peroneal muscular atrophy; with a critical review of the problems of 'intermediate forms' in the degenerative disorders of the central nervous system. *Brain*, **71**, 416-433.

ROUSSY, G. and LÉVY, G. (1926) Sept cas d'une maladie familiale particulière: troubles de la marche, pieds bots et aréfléxie tendineuse généralisée avec, accessoirment, légère maladresse des mains. *Revue Neurologique*, **1**, 427-450.

SCHWARTZ, G. A. and YANOFF, M. (1965) Lafora's disease. *Archives of Neurology, Chicago*, **12**, 172-188.

SHEPHERD, M. (1955) Report of a family suffering from Friedreich's disease, peroneal muscular atrophy, and schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry*, **18**, 297-304.

SKRE, H. (1975) Friedreich's ataxia in Western Norway. *Clinical Genetics*, **7**, 287-298.

—— and LÖKEN, A. C. (1970) Myoclonus epilepsy and subacute presenile dementia in heredo-ataxia. *Acta Neurologica Scandinavica*, **46**, 18-42.

SPILLANE, J. D. (1940) Familial pes cavus and absent tendon jerks: its relationship with Friedreich's disease and peroneal muscular atrophy. *Brain*, **63**, 275-290.

STEPHENS, J., HOOVER, M. L. and DENST, J. (1958) On familial ataxia, neural amyotrophy, and their association with progressive external ophthalmoplegia. *Brain*, **81**, 556-566.

THOMAS, P. K., CALNE, D. B. and STEWART, G. (1974) Hereditary motor and sensory polyneuropathy (peroneal muscular atrophy). *Annals of Human Genetics, London*, **38**, 111-130.

TILBERY, C. P., ALTIMARI, D. C., GAGLIARDI-FERREIRA, L. C. and NIETO, J. L. A. (1972) Associação na mesma familia das doenças de Charcot-Marie-Tooth e de Friedreich. *Arquivos Neuro-Psiquiatria (Sao Paulo)*, **30**, 158-165.

TUKEL, K. and ÇALISKAN, A. (1964) L'étude électroencéphalographique d'une famille dont deux membres sont atteints d'épilepsie myoclonique d'Unverricht-Lundborg. *Revue Neurologique*, **110**, 231-246.

YAMAMOTO, A., ADACHI, S., KAWAMURA, S., TAKAHASHI, M., KITANI, T., OHTORI, T., SHINJI, Y. and NISHIKAWA, M. (1974) Localised β-galactosidase deficiency. *Archives of Internal Medicine*, **134**, 627-634.

ZIEGLER, D. K., VAN SPEYBROECH, N. W. and SEITZ, E. F. (1974) Myoclonic epilepsia partialis continua and Friedreich ataxia. *Archives of Neurology, Chicago*, **31**, 308-311.

(*Received February 21, 1978*)

Brain (1978), **101**, 473–493

SENSORY ACTION POTENTIALS AND BIOPSY OF THE SURAL NERVE IN NEUROPATHY

by F. BEHSE *and* F. BUCHTHAL

(From the Institute of Neurophysiology, University of Copenhagen and the Laboratory of Clinical Neurophysiology of The Rigshospital, Copenhagen, Denmark)

INTRODUCTION

THE aim of this study was to investigate when slowing in conduction in peripheral neuropathy could be accounted for by axonal degeneration and when by demyelination (for references *see* Gilliatt 1973). For this purpose we review the relation of histological and electrophysiological findings in the sural nerve in a previously reported series of patients with neuropathy (Buchthal and Behse, 1977; Behse and Buchthal, 1977*a*, *b*; Behse, Buchthal, Carlsen and Knappeis, 1972; Behse, Buchthal and Carlsen, 1977) and in 66 other patients including 9 patients with unusual types of neuropathy. Among our patients, we found a number in whom the slowing in conduction could be accounted for neither by loss of large fibres nor by demyelination, and some other factor has to be assumed. Moreover, electrophysiological findings in the sural nerve were compared with those in the superficial peroneal and the median nerve to test whether findings in the sural nerve were representative.

PATIENTS

The material comprises 167 consecutive patients with polyneuropathy of different ætiology in whom a biopsy of the sural nerve was obtained (Table 1). Sixty per cent of the patients were males and 40 per cent females. Half of the patients were 40–60 years old. Neurological findings of most patients are summarized in Table 2; those patients with the less usual types of neuropathy are described on pp. 483–489. A probable ætiology was found in 85 per cent of the patients, often not until a follow-up examination was performed (49 patients). Of the 25 patients in whom the ætiology remained unknown, 16 had discrete neurological signs (Table 2); 12 of these had palsy referable to a single nerve (Buchthal and Behse, 1978).

METHODS

The methods have been described (Buchthal and Rosenfalck 1966, 1971; Behse and Buchthal, 1971; Buchthal and Behse, 1977). In brief, sensory conduction and the amplitude of the sensory potentials were determined along the following segments of the nerves: the sural nerve, from malleolus lateralis

TABLE 1. 167 PATIENTS WITH POLYNEUROPATHY

Acquired neuropathy of different ætiology	*No. of patients*	*Hereditary neuropathy*	*No. of patients*
Diabetic	12	Peroneal muscular atrophy	
Post-infectious	14	neuronal type	19
Alcoholic	38	hypertrophic type	10
Post-gastrectomy	6	*neuronal 'plus'	9
Paraneoplastic	4	Spino-cerebellar ataxia	3
Collagen disease	3	Hered. liability to pressure palsies	10
Uræmic	2		
Lead intoxication	9		
Hepatic	1		
B_{12} Malabsorption	1		
Acute interm. porphyria	1		
Unknown	25		

* Peroneal muscular atrophy of the neuronal type plus other forms of involvement of the central nervous system.

TABLE 2. INCIDENCE OF MAIN NEUROLOGICAL FINDINGS IN PATIENTS WITH POLYNEUROPATHY OF DIFFERENT ÆTIOLOGY

	Alcoholic	*Diabetic*	*Ætiology[1] unknown*	*Post-infectious*	*PMA-N[2]*	*PMA-H[3]*	*Hered. liab.[4] press. pals.*
No. of patients	37	12	16	14	19	10	10
Weakness (< 4)			Percentage of patients				
Lower extremities	51	33	0	71	95	90	20
Upper extremities	27	25	13	57	16	70	10
Isolated palsy	3	25	75	7	0	0	100
Tendon jerks, Depression or loss							
Ankle	89	100	69	100	100	100	50
Knee	65	75	50	93	53	100	40
Arms	54	83	44	79	21	100	70
Sensory impairment							
Paræsthesia	71	83	44	79	0	0	20
Pain	16	67	19	7	0	0	0
Touch, pin-prick	86	83	19	71	89	78	40
Vibration	74	75	19	83	78	89	10

[1] Discrete signs and symptoms. [2] Peroneal muscular atrophy, neuronal type. [3] Peroneal muscular atrophic, hypertrophic type. [4] Hereditary neuropathy with liability to pressure palsies.

to 12 to 15 cm proximal to it ('midcalf') or to fossa poplitea; the superficial peroneal nerve, from the superior retinaculum at the ankle to the capitulum fibulæ; the tibial nerve, from the first toe to the medial malleolus; the median nerve, from digit I and digit III to wrist.

Motor conduction velocities and motor latencies were determined along the peroneal nerve, and the distal segment of the tibial and the median nerves. The surface temperature of the extremity was kept at 36 to 37° C.

For the histological study 3 cm of the sural nerve were removed *in toto*, just proximal to the lateral malleolus, and prepared as described for the measurement of the total number of myelinated fibres, their size distribution and the numbers of groups of 3 or more regenerating fibres ('clusters') (Behse *et al.*, 1972, 1974; Behse and Buchthal, 1977*b*).

From each of 95 nerves, 30 to 70 myelinated fibres more than 7 μm in diameter were teased over a length of 5 to 10 mm (Vizoso and Young, 1948). The incidence per number of teased fibres of the following abnormalities was determined (Behse and Buchthal 1977*b*): (a) segmental demyelination; (b) widening of the nodal gap to more than 10 μm and paranodal demyelination over a length of up to 300 μm; (c) segmental remyelination, two or more short, often thinly myelinated segments between segments of normal length; (d) solitary intercalated segments, that is, remyelination secondary to paranodal demyelination; (e) regenerated fibres—all internodal segments were short (0·2 to 0·6 mm) and had a disproportionately thick diameter.

RESULTS

Are Electrophysiological Findings in the Sural Nerve Representative of Findings in other Nerves?

(1) Maximum conduction velocity along the sural nerve was compared with that along the corresponding segment of the superficial peroneal nerve and with the sensory velocity along the distal segments of the median nerve (fig. 1). In three-quarters of the patients, the sensory conduction velocity was similar along the three nerves. In one-quarter slowing along the superficial peroneal nerve occurred more frequently than along the sural nerve and least frequently along the median nerve.

(2) The amplitude of the sensory potential was equally often diminished (51 per cent) or normal (23 per cent) in the superficial peroneal nerve and in the same segment of the sural nerve. In 13 per cent of the patients the amplitude of the potential recorded from the superficial peroneal nerve was normal whereas that from the sural nerve was abnormal or *vice versa*. The percentage diminution was similar in both nerves. In 20 per cent of the patients the amplitude of the sensory potential in the distal segment of the median nerve was normal when it was abnormal in the intermediate segment of the sural nerve, whereas the reverse was the case in only 5 per cent of the patients. The sural nerve was more apt to be severely involved than the median nerve, the amplitude being less than 10 per cent of normal in half the sural and in one-third of the median nerves (fig. 7).

Histological Findings

(1) In most nerves from patients with alcoholic and diabetic neuropathy and in patients with the hypertrophic type of peroneal muscular atrophy, the number

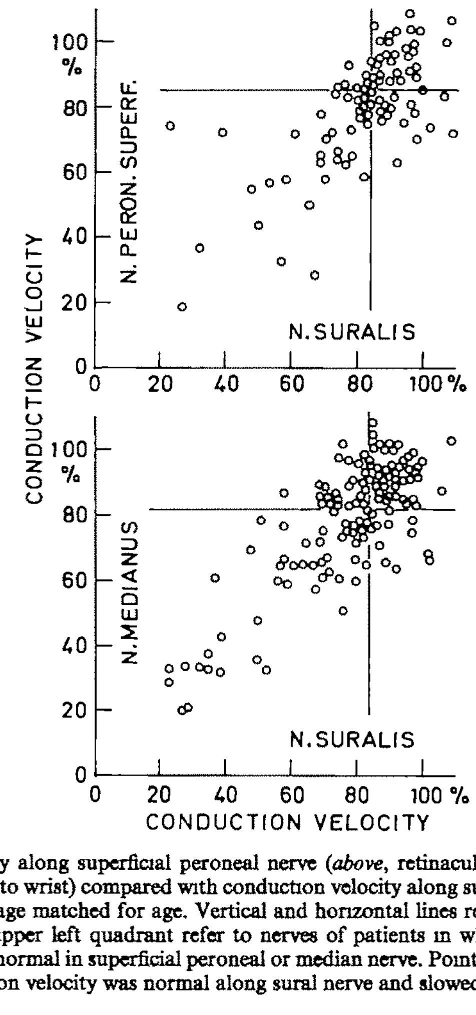


FIG. 1. Conduction velocity along superficial peroneal nerve (*above*, retinaculum to capitulum fibulæ) and median nerve (*below*, digit III to wrist) compared with conduction velocity along sural nerve. Velocities are given as percentage of normal average matched for age. Vertical and horizontal lines represent the lower 95 per cent confidence limits. Points in upper left quadrant refer to nerves of patients in whom conduction velocity was slowed along sural nerve and normal in superficial peroneal or median nerve. Points in lower right quadrant refer to patients in whom conduction velocity was normal along sural nerve and slowed along superficial peroneal or median nerve.

of large fibres ($> 7\ \mu m$ in diameter) was diminished to the same extent as the number of small fibres ($< 7\ \mu m$ in diameter, fig. 2). When the number of large fibres was diminished and that of small fibres was normal or slightly diminished (neuronal type of peroneal muscular atrophy, neuropathy associated with collagen disease, post-infectious polyneuropathy and neuropathy of unknown ætiology), signs of regeneration were prominent and could, at least in part, account for the lesser diminution in the number of the small fibres.

(2) Abnormalities in the myelin sheath were determined in teased fibres, per number of internodal segments and per number of fibres. The proportion of abnormalities was the same by the two methods, and all data in this study refer

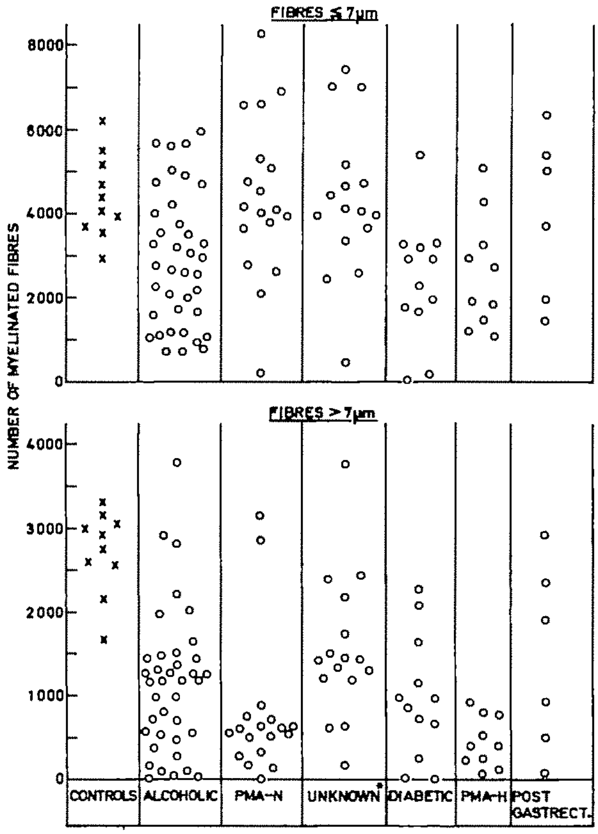


FIG. 2. Number of small (diameter ≤ 7 µm) and of large (diameter > 7 µm) fibres in the sural nerve of patients with polyneuropathy of different ætiology compared with controls. × = discrete signs and symptoms, *see* Table 2.

to the incidence of abnormalities per number of teased fibres. In the seven nerves from controls (14–54 years old) from which teased fibres were obtained, demyelination was absent; paranodal and segmental remyelination and regenerated fibres occurred in at most 20 per cent of the teased fibres (fig. 3).

Segmental demyelination was found in 27 per cent of the nerves of patients with neuropathy. It usually occurred in less than 10 per cent of teased fibres, except in the hypertrophic type of peroneal muscular atrophy (Behse and Buchthal, 1977*a*), in the neuropathy after gastrectomy (Behse and Buchthal, 1977*b*), and in one patient with neuropathy of unknown ætiology. In these conditions segmental demyelination was present in 30 to 100 per cent of the fibres. Paranodal demyelination occurred in a quarter of the nerves, the incidence rarely exceeding 15 per cent. Segmental remyelination was increased above the level in controls in 33 of the nerves, but only in five nerves did more than half of the fibres show this abnormality. The most frequent abnormality, seen in half the nerves, was paranodal remyelination, i.e., solitary intercalated segments present in less than 20 per cent

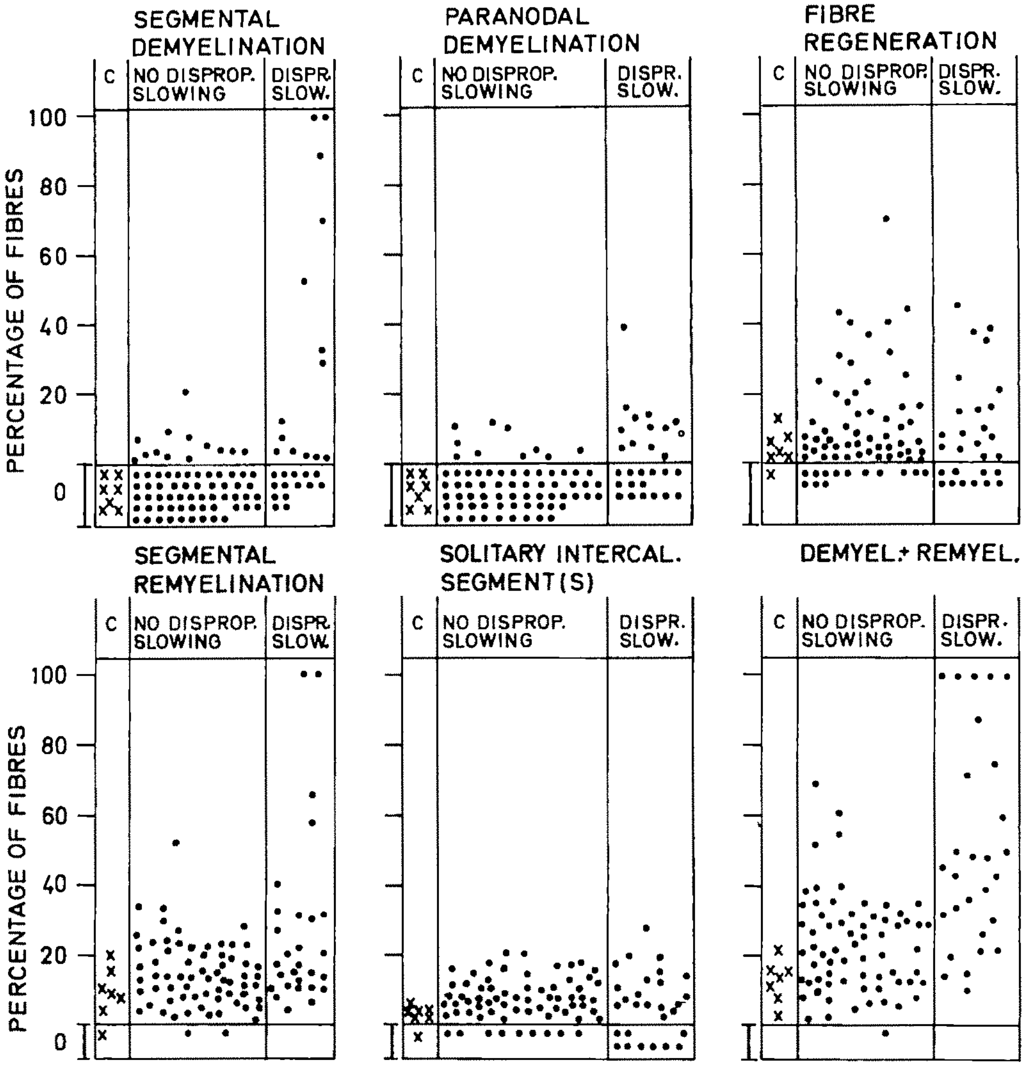


FIG. 3. Incidence of different myelin abnormalities and of regenerated fibres among teased fibres from 7 controls (C, X) and from 95 nerves of patients with acquired or heredodegenerative polyneuropathy (●), grouped according to the presence or absence of disproportionate slowing in conduction velocity (for definition *see* p. 480).

of teased fibres. The incidence of regenerated fibres was increased in one-third of the nerves (fig. 3).

Nerve Conduction as Related to Histological Findings

In normal sural nerve and in nerves with loss of the largest fibres but no myelin abnormalities, the conversion factor to calculate the maximum conduction velocity from the largest myelinated fibres was 4·3, SD 0·3. The conduction velocity was calculated from that class of fibres of the largest diameter that contained at least

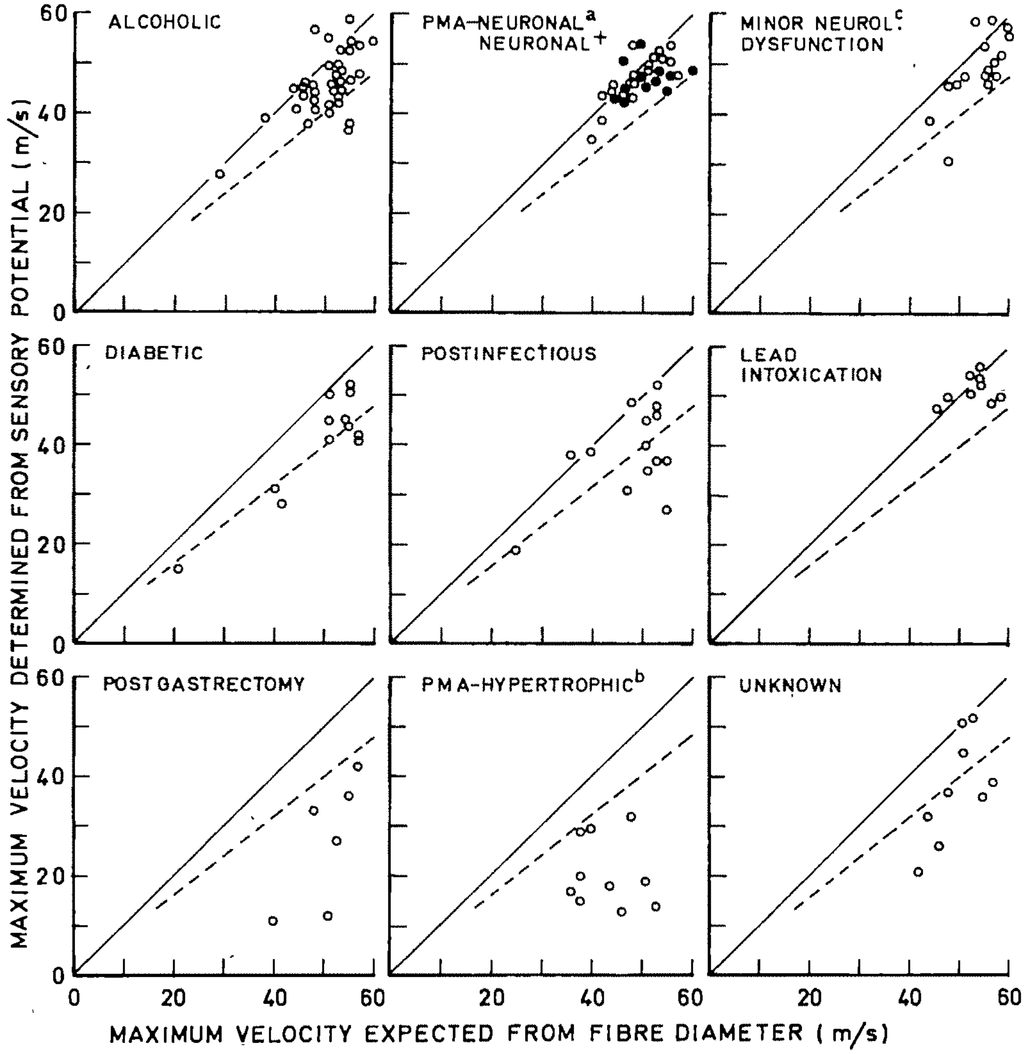


FIG 4. Maximum conduction velocity determined from sensory potential of sural nerve as a function of velocity expected from diameter of largest myelinated fibres of the same nerve in patients with polyneuropathy of different ætiology. Full line represents equality between recorded and expected velocity. Loss of large fibres can explain slowing in conduction when recorded velocity is within 20 per cent of that expected from fibre diameter (dashed line, lower limit of normal range). When deviation between recorded and expected velocity exceeds 20 per cent, slowing in conduction has causes other than fibre loss (a) peroneal muscular atrophy of neuronal type; ● = nerves from patients who in addition have other forms of involvement of the c.n s or spinocerebellar ataxia; (b) peroneal muscular atrophy of hypertrophic type; (c) nerves from patients with discrete signs of neuropathy of unknown ætiology (*see* Table 2).

ten fibres since activation of at least ten fibres of the same diameter was required to obtain a response that could be distinguished from noise when 500 to 2000 responses were averaged (Buchthal, Rosenfalck and Behse, 1975). When the diminution in conduction velocity was within 20 per cent of that to be expected from the diameter of the largest fibres (the scatter in controls), it could be accounted for by loss or block of large fibres. This mechanism explained the slowing in conduction in most patients with alcoholic neuropathy (Behse and Buchthal, 1977*b*), in the neuronal type of peroneal muscular atrophy (Buchthal and Behse, 1977), in lead intoxication and in nerves from patients with discrete signs of peripheral neuropathy of unknown ætiology—'minor neurological dysfunction' (fig. 4). In patients with the hypertrophic type of peroneal muscular atrophy (Buchthal and Behse, 1977), in post-gastrectomy neuropathy (Behse and Buchthal 1977*b*), and in some of the patients with diabetic (Behse *et al.*, 1977) and post-infectious neuropathy and with neuropathy of unknown ætiology, slowing in conduction exceeded that to be expected from the diameter of the largest fibres by more than 20 per cent, 'disproportionate slowing' (fig. 4).

When and to what Extent Was Slowing in Conduction Velocity Associated with a high Incidence of Segmental or Paranodal Demyelination?

Slowing in conduction (<45 m/s) was present in 43 nerves (fig. 5) from which teased fibres were obtained. In eighteen nerves slowing was moderate (35 to 44 m/s) and as to be expected from the loss of the largest fibres; with one exception, the incidence of demyelination was negligible and comprised less than 3 per cent of teased fibres. In sixteen nerves with conduction velocities of 26 to 44 m/s, neither axonal loss nor demyelination could account for the slowing; conduction velocity was 22 to 44 per cent slower than to be expected from the largest fibres in the biopsy, and demyelination, present in eleven nerves, occurred in at most 16 per cent of the teased fibres. In nine nerves the incidence of demyelination comprised 30 to 100 per cent of the teased fibres and the conduction velocity was 12 to 30 m/s; axonal loss could not account for the marked slowing. When the rate of conduction along all nerves examined in the individual patient was considered (fig. 6), disproportionate slowing along sural nerves with little or no demyelination was associated with less slowing also in other nerves than when there was demyelination. Disproportionate slowing along all nerves was then similar to or slightly more marked than proportionate slowing. Three of the patients with disproportionate slowing and little or no demyelination had diabetic neuropathy; in 5 the ætiology of the neuropathy was unknown and the remaining 8 patients had neuropathy of widely differing ætiologies (fig. 6).

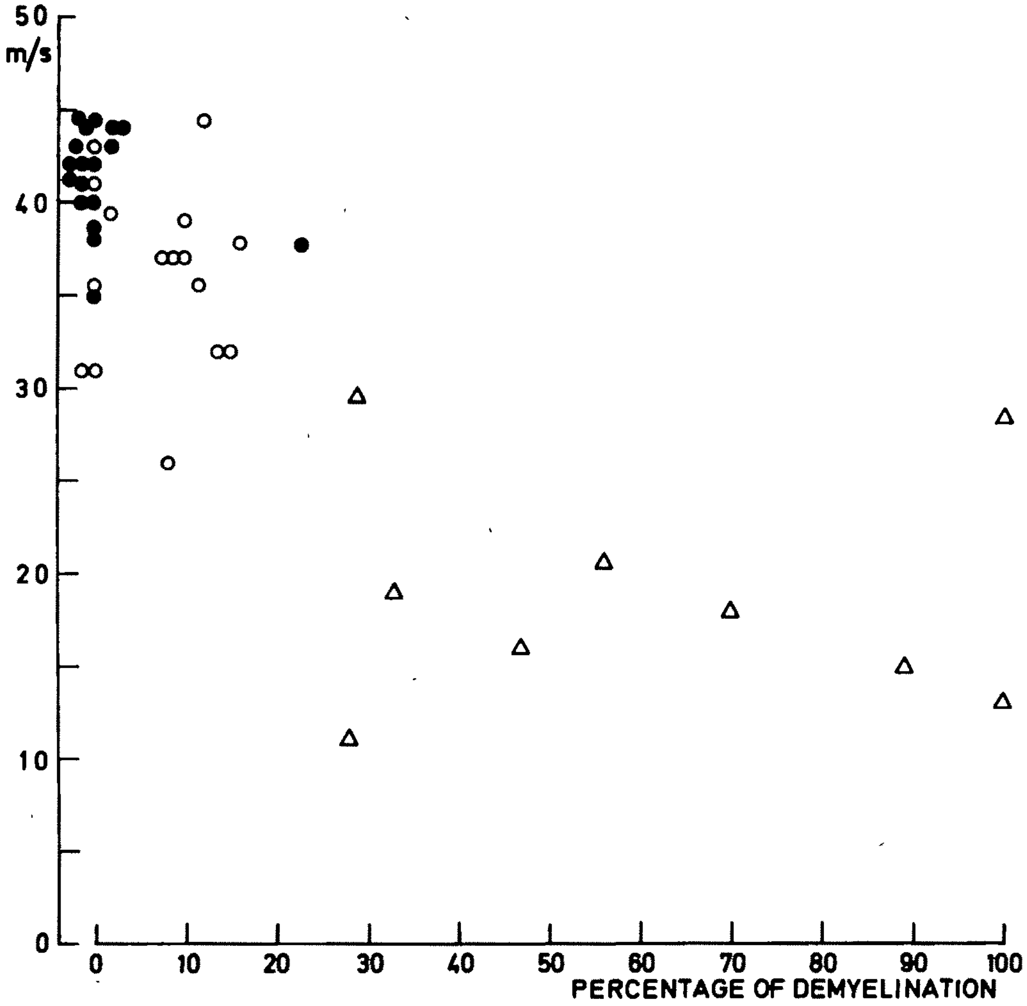


FIG. 5. Conduction velocity as a function of the incidence of segmental and paranodal demyelination in teased fibres of 43 sural nerves with slowed conduction. ● = 18 nerves in which slowing in conduction was as to be expected from the diameter of the largest fibres. △ = 9 nerves with a high incidence of demyelination and 'disproportionate slowing' (p. 480). ○ = 16 nerves with 'disproportionate slowing' and low incidence of fibres with demyelination.

The Amplitude of the Sensory Potential as Related to Histological Findings

The main components of the sensory potential derive from large fibres ($> 7\ \mu m$ in diameter); and the peak-to-peak amplitude is determined by fibres of more than $9\ \mu m$ in diameter (Buchthal *et al.*, 1975). When nerves were excluded which showed 'disproportionate slowing', the peak-to-peak amplitude of the sensory potential increased linearly with the number of fibres more than $9\ \mu m$ in diameter ($P < 0{\cdot}001$, fig. 7). The number of large myelinated fibres and the amplitude of sensory

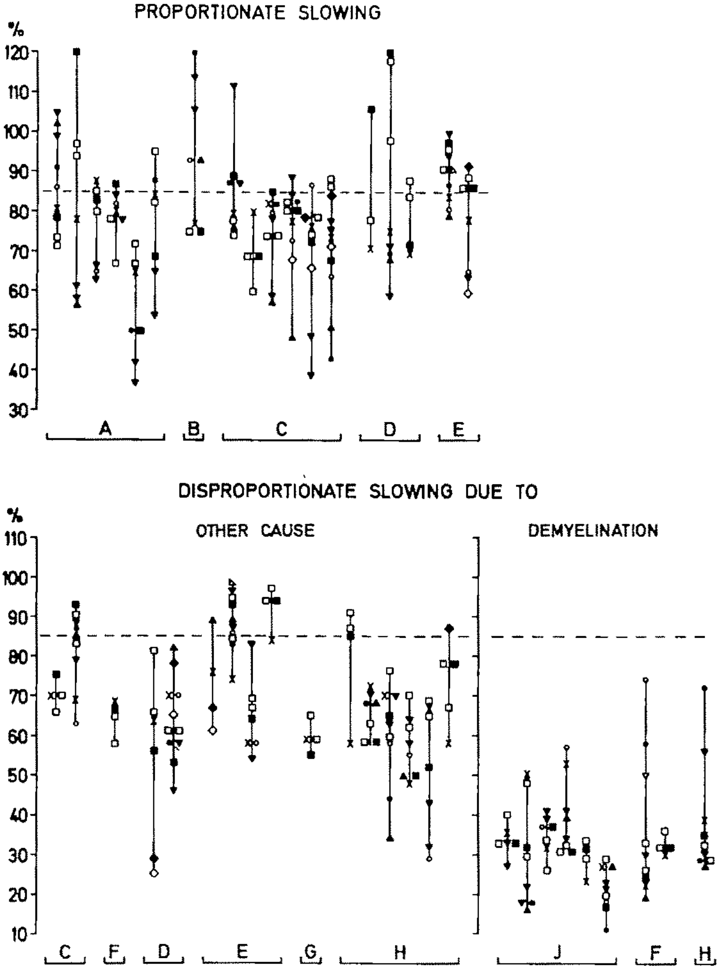


FIG. 6. Ætiology of neuropathy and sensory and motor conduction along nerves examined from 43 patients with slowed conduction along the sural nerve (fig 5). Conduction velocity is given as percentage of the normal average matched for age; the motor latencies are given as reciprocal latencies. Each vertical line connects findings in different nerves in the individual patient; dashed line represents lower 95 per cent confidence limit of normal A = peroneal muscular atrophy, neuronal type. B = spinocerebellar ataxia (Friedreich) C = alcoholic neuropathy. D = post-infectious neuropathy. E = diabetic neuropathy. F = post-gastrectomy neuropathy G = paraneoplastic neuropathy H = neuropathy of unknown ætiology. J = Peroneal muscular atrophy, hypertrophic type. Sensory nerves: sural (X), superficial peroneal (O), distal tibial (◇), saphenus (△), distal median, (□, digits I and III). Motor nerves, velocity: deep peroneal (●). Motor latencies m tibialis anterior and m. peroneus longus (▼), m. extensor digitorum brevis (▲), m. flexor hallucis brevis (◆), m. abductor pollicis brevis (■).

potentials was equally diminished, whether slowing was due solely to loss of the large fibres, or in addition to other causes—'disproportionate slowing' (fig. 8). In half the patients with polyneuropathy, the sensory potential of the sural nerve was split up into more components than in controls. The increased split-up was particularly frequent when potentials had an amplitude less than 5 per cent of normal. From the shape of the potential it could not be deduced whether slowing was due to loss of fibres, to regeneration or to displacement of normally fast components to slower velocities (Buchthal and Rosenfalck, 1971).

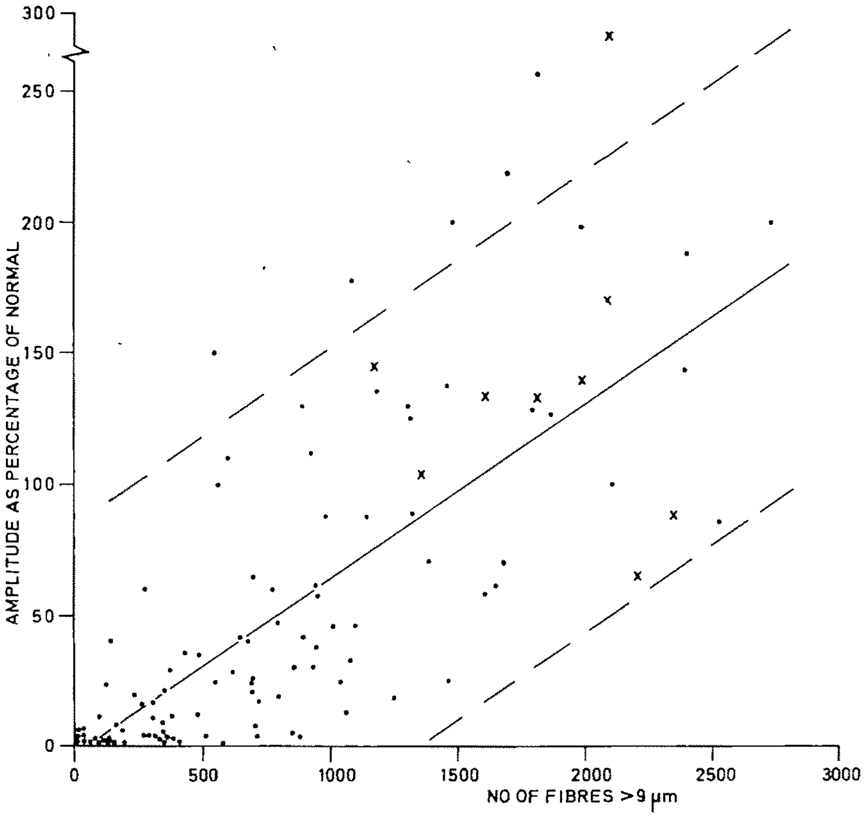


FIG. 7. Amplitude of sensory potential in sural nerve, given as percentage of the normal average matched for age, as a function of number of myelinated fibres more than 9 μm in diameter in patients with acquired and heredodegenerative polyneuropathy (●) and in controls (X). Full line is regression line ($P < 0{\cdot}001$); dashed lines indicate 95 per cent confidence limits. Nerves along which conduction was slowed by 20 per cent or more than to be expected from the diameter of the largest fibres are not included.

Less Usual Types of Neuropathy

Based on the relation of nerve biopsy and conduction velocity described above in some common types of human polyneuropathy, we have applied these concepts to findings in 9 patients with less usual types of neuropathy. Though there is an extensive literature on each of them (*see* Bradley 1974, Asbury 1975, Conn and

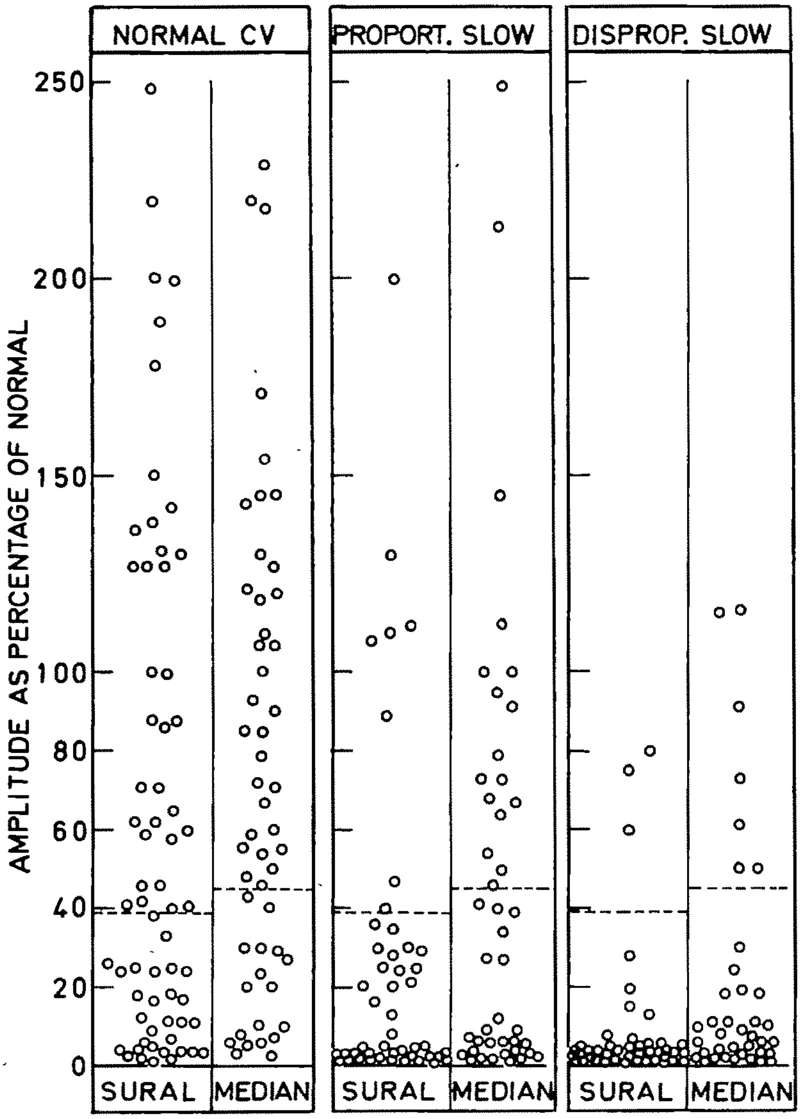


FIG. 8. Amplitude of sensory potential of sural and median nerves as percentage of mean amplitude in controls matched for age. *Left*, sensory amplitudes from nerves of patients with normal conduction velocity along sural nerve. *Middle*, nerves with slowing in conduction as expected from diameter of largest fibres in sural nerve. *Right*, sensory amplitude in nerves with 'disproportionate slowing' along sural nerve (p. 480) Dashed lines indicate 95 per cent confidence limits for normal amplitudes of sural and median nerves.

Dyck 1975, McLeod 1975, Ridley 1975) data in which quantitative nerve biopsy findings were related to studies of conduction along the same nerve have not been reported.

The polyneuropathy was associated with malignant neoplasm in 4 patients; with rheumatoid arthritis in 2 patients; with polyarteritis nodosa in 1 patient; with acute intermittent porphyria in 1 patient and with chronic liver disease in 1 patient.

Neuropathy Associated with Malignant Neoplasm

(1) *Sensorimotor neuropathy*

The patient was a 48-year-old female who was operated on for cancer of the uterus six months after the onset of neuropathy. She had marked weakness in the distal and proximal muscles of the arms and legs; the only sensory impairment was paræsthesia and absent perception of vibration in the feet. Ankle jerks were absent, knee jerks normal, and tendon jerks in the arms were weak. Standard laboratory tests were normal.

Sensory conduction was slowed to 60 per cent of normal in the sural and median nerves, and the amplitude of the sensory potentials was diminished to 4 (sural) and 20 per cent (median nerve) of normal. The slowing in sensory conduction could be explained neither by axonal degeneration nor by demyelination (Table 3). The incidence of fibres with paranodal and segmental remyelination was twice that in controls.

TABLE 3. HISTOLOGICAL FINDINGS IN SURAL NERVES OF PATIENTS WITH LESS USUAL TYPES OF NEUROPATHY

		No. myelin fibres			*Percentage of teased fibres with*				
Polyneuropathy associated with	*Endoneur. area (mm²)*	*all*	*>7 µm*	*No. of clusters*	*paranod. demyel*	*segment. demyel.*	*split intercal. segm.*	*segment. remyel.*	*Percentage of teased regen. fibres*
Malignant neoplasm									
Patient No. 1	0·89	4,050	911	45	14·0	0	12·0	22·0	0
2	1·43	7,500	2,640	78	—	—	—	—	—
3a	1·59	9,730	3,500	52	0	0	3·6	1·8	31
3b	1·13	6,400	1,860	64	0	0	13·6	16·8	0
Collagen disease									
1*	>0·4	2,400*	108*	25*	—	—	—	—	—
2	0·49	320	2	0	—	—	—	—	—
3**	1·11	3,500	2	71	—	—	—	—	—
Acut. intermitt. porphyria	1·42	7,160	1,547	132	0	0	10	12	8
Liver cirrhosis	1·27	3,850	1,213	48	3·6	5·4	1·8	3·6	28·6
Controls n = 10 (teased fibres, n = 7)	0·65 1·26	5,200 9,500	1,650— 3,300	0–38	0	0	0–6·4	5–20	0–13

* Branch of sural nerve, data given per mm². ** Polyarteritis nodosa.

(2) *Sensory neuropathy*

The patient was a 54 year-old female in whom an ovarian cancer was removed six months before signs and symptoms of neuropathy were noticed. There was no weakness or wasting, but on electromyography there were fibrillations and signs of loss of motor units in the anterior tibial and abductor pollicis brevis muscles. The patient complained of paræsthesia in the feet, where cutaneous sensation and the perception of vibration were diminished. Tendon jerks were absent or weak in the lower extremities.

Sensory and motor conduction velocity along nerves of the upper and lower limbs and the amplitude of the sensory potentials were borderline. The only histological abnormality in cross-sections was an increased number of clusters of regenerating fibres (Table 3); teased fibres were not obtained.

(3) *Motor neuropathy*

(a) The 48-year-old patient had a cancer of the portio uteri diagnosed three years after the onset of neuropathy. She had marked and rapidly progressive weakness in the distal and proximal muscles of the legs, later extending to the arms. Cutaneous sensation and perception of vibration were normal, as were standard laboratory tests. The patient died six years after the onset of neuropathy.

Electromyography was compatible with involvement of the lower motor neurone but not with motor neurone disease. Sensory and motor conduction were normal. The histological abnormalities in the nerve were a slight increase in endoneurial area and signs of regeneration of myelinated fibres (Table 3).

(b) In a 48 year-old man an adenocarcinoma of the rectum was removed one year after the onset of neuropathy. Distal muscles of the lower extremities were weak, more so on the left. Tendon jerks were absent or weak.

Though cutaneous sensibility and the perception of vibration were normal, sensory conduction along the sural nerve was slightly slowed, and the sensory potential was split up. The maximum conduction velocity was as to be expected from the diameter of the largest myelinated fibres. There was a slight decrease in the number of myelinated fibres of more than 9 μm in diameter; the only abnormality in teased fibres was an increased incidence of fibres with intercalated segments (Table 3).

These examples illustrate that there was no uniform type of involvement of peripheral nerves in the patients with paraneoplastic neuropathy that we have examined.

Neuropathy Associated with Collagen Disease

Two women, 67 and 55 years old, with sero-positive rheumatoid arthritis had neuropathy which had lasted for two months (Patient 1) and ten years (Patient 2). Patient 1 had marked weakness of distal and proximal muscles of the arms and legs, and both patients had paræsthesia and impairment of cutaneous and vibratory sensibility. Patient 3, a 48-year-old man, had signs and symptoms of polyarteritis nodosa with febrile episodes, eosinophilia, involvement of the respiratory and gastrointestinal tracts, and of the central nervous system Renal angiography showed many microaneurysms peripherally in the small arteries. Biopsy of the medial vastus muscle showed necrotizing arteritis and collections of leucocytes (lymphocytes and eosinophils) about the vessels; the muscle tissue was normal. For the past two years he had also signs of neuropathy with severe sensorimotor impairment and absent tendon jerks.

Nerve conduction and histological findings were similar in the 3 patients: sensory conduction velocity along the sural nerve was diminished as would be expected from the diameter of the largest fibres (37, 20, 34 m/s); the amplitude of the sensory potentials was 1 to 4 per cent of normal. Large myelinated fibres were so nearly absent that teased fibres could not be obtained (Table 3). Electron microscopy, obtained in Patient 3, showed degeneration of unmyelinated fibres and proliferation of Schwann cells (Behse *et al.*, 1974).

Neuropathy Associated with Acute Intermittent Porphyria

The patient was a 49 year-old woman; several siblings of her mother had the disease. The first attack was characterized by abdominal pain, sudden onset of weakness of muscles in the upper and lower extremities, absent tendon jerks and dark-coloured urine.

Electromyography showed signs of chronic denervation and reinnervation, and the paresis recovered within two weeks. The next attack was twenty years later; she had weakness of the left forearm that recovered incompletely. An electrophysiological study and a nerve biopsy were performed six months after the last attack. There was weakness of distal muscles in the legs and arms but no sensory impairment; tendon jerks were diminished.

Sensory conduction velocity was borderline and as to be expected from the largest fibres found in the biopsy. The amplitude of the sensory potentials in the sural and the superficial peroneal nerve was 20 per cent of normal (fig. 9, left, inset, above).

The number of large myelinated fibres was slightly diminished, (fig. 9, left, above and below) and there were many clusters of regenerating fibres (Table 3). Teased fibres showed a slight increase in the incidence of paranodal remyelination. Eight months after the last attack weakness of the muscles of the forearm had improved and the amplitude of the sensory potential of the sural nerve (the nerve contralateral to the one from which a biopsy was obtained) was more than twice that found two months earlier. This increase exceeds the difference seen between the right and the left sural nerve and indicates that some myelinated fibres were activated that had been blocked two months earlier.

Neuropathy Associated with Cirrhosis of the Liver

The patient was a 69 year-old woman admitted to Medical Department A of the University Hospital (Professor N. Tygstrup). She had an infectious hepatitis when she was 39 years old and there was no history of alcoholism. Two years before admission she complained of itching and increasing fatigue. Blood studies showed anæmia, a moderate increase in the activity of aminotransferases and of alkaline phosphatase. Liver biopsy, performed six months later, showed evidence of mild portal fibrosis and inflammatory changes. A second liver biopsy, obtained eighteen months later, showed changes compatible with primary biliary cirrhosis, confirmed by the presence of mitochondrial antibodies, increased plasma gamma-M globulin and a 4- to 5-fold increase in the activity of alkaline phosphatase in the serum. There was little evidence of active liver impairment (normal alanine aminotransferase and serum bilirubin) and liver function was intact (normal serum albumin, prothrombin, galactose elimination capacity and clearance of antipyrin). There was no history of ascites or bleeding from œsophageal varices. For the past two years the patient had slight motor weakness, impaired co-ordination, diminished cutaneous sensibility and absent perception of vibration; tendon jerks were absent.

The amplitude of the sensory potentials in the superficial peroneal, the sural and the median nerves was less than 10 per cent of normal (fig. 9, right, inset, sural

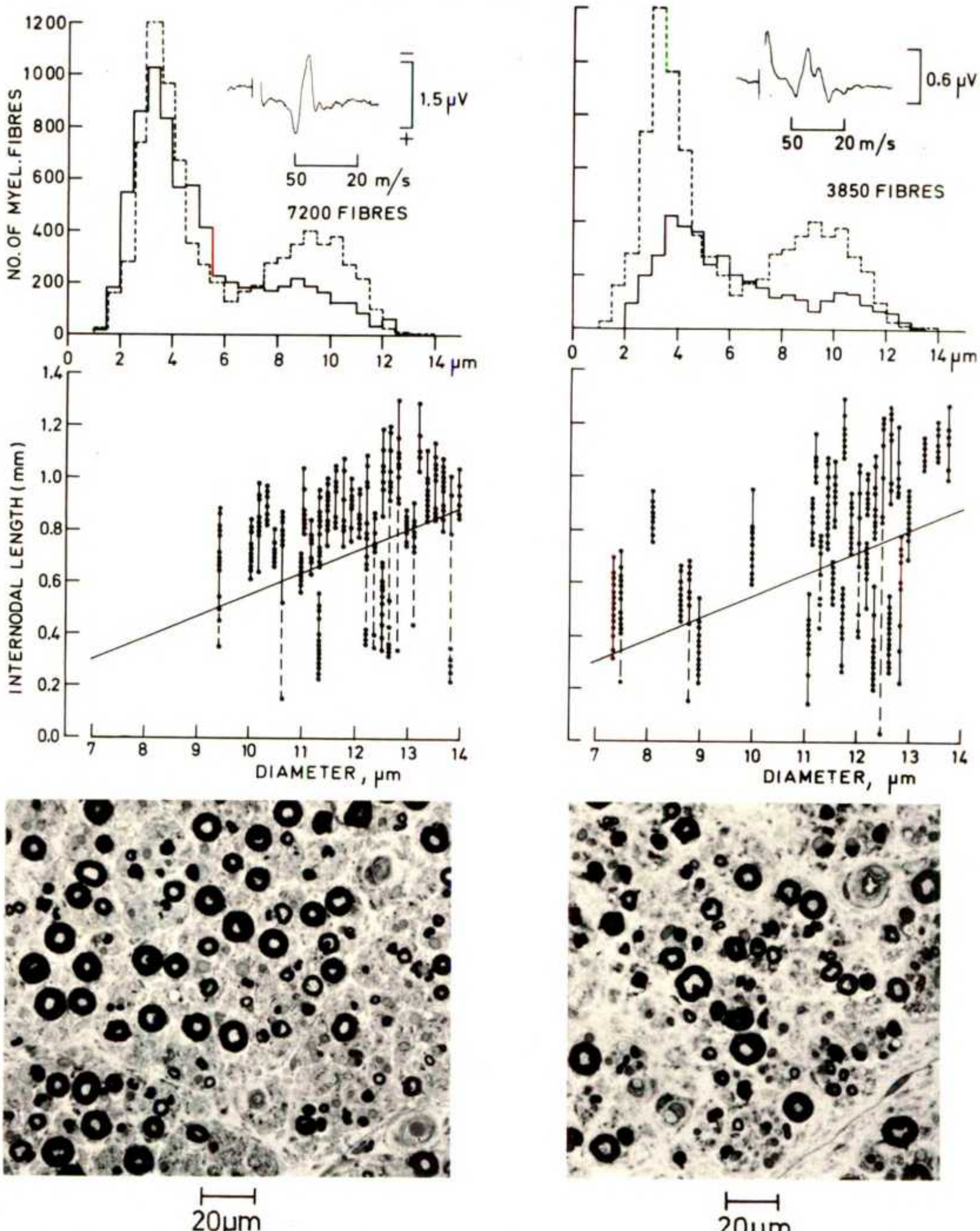


FIG. 9. Sensory conduction and histological findings in myelinated fibres from patient with neuropathy associated with acute intermittent porphyria (*left*) and with liver cirrhosis (*right*). *Above*, histograms of fibre diameter (dashed line = from normal nerve). Insets: Sensory potential of sural nerve. *Middle*, internodal length as function of diameter, plotted in 30 of 50 teased fibres for each nerve; incidence of abnormalities is given in Table 3. Oblique line indicates 95 per cent lower confidence limit of internodal length in normal nerve. Dashed lines indicate short remyelinated segments between segments of normal length. *Below*, a representative sample of cross-section of each nerve; method described in Behse and Buchthal (1977*b*).

nerve at midcalf). The conduction velocity along the sural nerve was borderline and as to be expected from the diameter of the largest fibres (fig. 9, right, above); 9 per cent of the teased fibres showed paranodal and segmental demyelination (Table 3). The number of large and small myelinated fibres was diminished by 40 per cent (fig. 9, right, above and below. Table 3) and that of unmyelinated fibres by 75 per cent (6,800 fibres). The incidence of unmyelinated fibres undergoing degeneration was twice that in controls (Dyck and Hopkins, 1972, Behse *et al.*, 1975).

DISCUSSION

About one-third of the 167 patients with polyneuropathy were seen repeatedly over the years. This explains why a probable ætiology was found in 142 of them. The incidence of polyneuropathy of unknown ætiology would be about doubled at the time of the first study. The material contains most of the varieties of neuropathy encountered in an industrialized country and in a temperate climate except that idiopathic polyradiculoneuropathy is under-represented, since such patients were usually segregated in the hospital for infectious diseases.

In the description of nerve conduction studies, the main emphasis has been on findings in the sural nerve since they could be compared with histological findings. Under ideal conditions of recording, the amplitude of the sensory potentials is proportional to the number of large fibres activated. The validity of this assumption was demonstrated in a simple experiment: the amplitude of the sensory potential recorded at wrist and evoked by the simultaneous stimulation of two digits was equal to the algebraic sum of the sensory potentials evoked by separate stimuli to digit II and digit III (Buchthal and Rosenfalck, 1966). In polyneuropathy the amplitude of the sensory potentials was in the main related to the number of large myelinated nerve fibres ($P < 0{\cdot}001$) though the scatter was considerable, due to (i) differences in the distance between the near-nerve electrode and the nerve trunk; (ii) fibres included in the count that failed to conduct; (iii) the individual variation in the number of fibres of 9 μm or more, varying in 10 nerves from controls from 1100 to 2300; (iv) the amount of fat in the tissue surrounding the nerve: in 35 per cent of 54 normal children aged 4 years or less, the amplitude of the sensory potential exceeded the upper 95 per cent confidence limit of the amplitude in nerves from adults (unpublished). Summation of the components of the split-up potential did not diminish the scatter of amplitude as a function of fibre number. Notwithstanding the scatter, the amplitude of the sensory potentials was a gauge of the loss of large myelinated fibres: three-quarters of the nerves with a diminished number of large fibres had a sensory potential of diminished amplitude, whereas 90 per cent of the nerves with a normal number of large fibres had sensory potentials of normal amplitude.

The amplitude of the sensory potential was a more sensitive indicator of abnormality than was conduction velocity. Of 111 sural nerves with mainly axonal degeneration, 62 per cent had a diminished amplitude of the sensory potential and 42 per cent had slowing in conduction. In fact, the maximum conduction velocity remained within the range of normal when 10 to 20 of the large fibres conducted at a normal rate.

That 23 of 33 patients, in whom conduction and sensory amplitude were normal in the sural nerve, showed mild histological abnormalities indicates that the histological investigation was more sensitive than the study of conduction. The reverse, abnormal conduction velocity or amplitude of the sensory potentials and normal histology of the sural nerve, was not seen.

The relation of histological abnormalities to slowing in conduction was evaluated in the 43 nerves with slowing from which teased fibres were obtained. In 18 nerves slowing was moderate and was due to axonal loss, and demyelination occurred in less than 3 per cent of teased fibres. Conversely, in 9 nerves, axonal loss could not explain the marked slowing; demyelination was seen in many teased fibres and could probably account for the marked slowing. There remain 16 nerves (37 per cent) in which slowing could be explained neither by fibre loss nor by the incidence of demyelination present in at most 20 per cent of the fibres.

In this connection the question arises whether findings obtained over 10 mm of 50 teased nerve fibres were representative for the 120 to 150 mm of the 100 to 3500 fibres over which conduction velocity was determined. The incidence of fibres with myelin abnormalities did not increase proportionately with the length over which the fibres were teased. Thus, in 16 nerves of patients with disproportionate slowing, the incidence of normal fibres, of fibres with myelin abnormalities and of myelin defects per fibre obtained over 5 mm of teased fibres was compared with that obtained over 10 mm of teased fibre. When teased over a length of 10 mm the incidence of abnormalities was 30 per cent higher instead of doubled. By extrapolation[1] this suggests that the incidence of fibres with demyelination would increase from, for example, 20 per cent in 10-mm-long teased fibres to 50 per cent over a 130-mm-long portion of the nerve, that is, with this assumption half of the fibres would not have segments with demyelination.

Teased fibres were obtained from 3 to 5 different fascicles. This probably compensates for the differences in myelin abnormalities in different fascicles. In 8 nerves from lead-exposed men a second series of 50 fibres was teased (Dr. Galassi). The incidence of myelin abnormalities was the same as in the first series. Thus, although there is no definite proof, it seems likely that so many fibres had an intact myelin sheath that demyelination did not account for the slowing.

Remyelination occurred as frequently in nerves with as in those without slowing and can therefore not explain the slowing in conduction.

We are still ignorant of the other cause of slowing when neither loss of fibres nor demyelination can explain it. There are other conditions in which slowing occurs in the absence of structural changes: (i) in the hypoxic segment of the nerve conduction decreased to 40 per cent of the pre-hypoxic level (Caruso, Labianca and

---

[1] The computer programme is available on request.

Ferrannini, 1973, Nielsen and Kardel 1974), whereas it regained normal velocity proximal to the hypoxic segment, indicating that there was true slowing before conduction was blocked (Behse and Buchthal, 1975). Presumably hypoxia prolonged the rate of rise of the nodal action current; (ii) in experimental diabetes (Sharma and Thomas, 1974, Sharma, Thomas and De Molina, 1977) and in galactosæmia (Sharma, Thomas and Baker, 1976), slowing in conduction has been found in the absence of fibre loss or other structural or ultrastructural changes.

Some kind of a functional defect in the nerve membrane may be co-existent with structural changes and may be more common than hitherto assumed. Thus, the defect may explain why in nerves with proportionate slowing the recorded velocity tended to be slightly lower than that calculated from diameter (fig. 4, upper row). Depending on the severity of the defect, nerves in alcoholic, diabetic or post-infectious neuropathy (fig. 6, C, D, E) may exhibit proportionate or disproportionate slowing. Disproportionate slowing due to the assumed functional defect of the membrane was less marked than the slowing due to extensive demyelination.

SUMMARY

In 167 consecutive patients with various types of neuropathy, the amplitude of the sensory potential and the maximum conduction velocity along the sural nerve were compared with conduction in other sensory nerves, and were related to structural changes revealed by nerve biopsy. Electrophysiological findings in the sural nerve were similar to those in the superficial peroneal and the median nerve, though the distal segment of the median nerve was normal in 20 per cent of the patients when it was abnormal in the sural nerve.

Quantitation of histological findings was a more sensitive method than the electrophysiological study in that two-thirds of 33 patients with normal electrophysiology in the sural nerve showed mild loss of fibres or signs of remyelination in teased fibres. The amplitude of the sensory potential was grossly related to the number of large myelinated fibres ($> 7\,\mu m$ in diameter). Considering the 95 nerves from which teased fibres were obtained, maximum conduction velocity was abnormal in half. In 18 of these nerves, slowing in conduction was due to axonal degeneration: the velocity was as to be expected from the diameter of the largest fibres in the biopsy ('proportionate slowing'). In 9 nerves slowing was severe and more marked than to be expected from loss of the largest fibres ('disproportionate slowing'); these nerves showed paranodal or segmental demyelination in more than 30 per cent of the fibres.

In 16 nerves from patients with neuropathy of different ætiology neither loss of fibres nor demyelination could explain the moderate slowing. The cause of slowing in these nerves is unknown; other conditions are referred to in which slowing in conduction cannot be attributed to morphological changes. Finally, electrophysiological and histological findings are reported in some patients

with neuropathy associated with malignant neoplasm, with rheumatoid arthritis, with polyarteritis nodosa, with acute intermittent porphyria and with cirrhosis of the liver.

ACKNOWLEDGEMENTS

We are indebted to the Department of Neurology of the Rigshospital and of the Municipal and County Hospitals, Copenhagen, for referring patients under their care, and to the staff of the Department of Neurosurgery of the Rigshospital, Copenhagen, for performing the sural biopsies. We thank S. Steenstrup, of the Institute of Physics II, for computing the increase in the incidence of nerve fibres with myelin abnormalities with increasing fibre length.

The work was supported by grants from the Muscular Dystrophy Associations of America, New York, and the Michaelsen Foundation, Copenhagen.

REFERENCES

ASBURY, A. K. (1975) Hepatic neuropathy. In: *Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas and E. H. Lambert. Philadelphia: W. B. Saunders, Vol. 2, pp. 993-998.

BEHSE, F. and BUCHTHAL, F. (1971) Normal sensory conduction in nerves of the leg in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 404-414.

—— —— (1975) Slowing in maximum nerve conduction velocity during acute hypoxia due to block of large fibres or to slowing along all fibres? Abstracts, 21st Scandinavian Congress of Neurology, June 11-14, Stockholm, p. 4. The abstracts will not be reprinted in the *Acta neur.* They have appeared as a little book prepared and printed by the Department of Neurology, Karolinska Hospital, Stockholm (no publisher).

—— —— and CARLSEN, F. (1977) Nerve biopsy and conduction studies in diabetic neuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 1072-1082.

—— —— —— and KNAPPEIS, G. G. (1972) Hereditary neuropathy with liability to pressure palsies. *Brain*, **95**, 777-794.

—— —— —— —— (1974) Endoneurial space and its constituents in the sural nerve of patients with neuropathy. *Brain*, **97**, 773-784.

—— —— —— —— (1975) Unmyelinated nerve fibres and Schwann cells of sural nerve in neuropathy. *Brain*, **98**, 493-510.

—— —— (1977*a*) Peroneal muscular atrophy (PMA) and related disorders. II. Histological findings in sural nerves. *Brain*, **100**, 67-85.

—— —— (1977*b*) Alcoholic neuropathy: Clinical, electrophysiological and biopsy findings. *Annals of Neurology*, **2**, 95-110.

BRADLEY, W. G. (1974) *Disorders of Peripheral Nerves*. Oxford: Blackwell, pp. 169, 172, 191, 193, 195, 265, 283.

BUCHTHAL, F. and BEHSE, F. (1977) Peroneal muscular atrophy (PMA) and related disorders. I. Clinical manifestations as related to biopsy findings, nerve conduction and electromyography. *Brain*, **100**, 41-66.

—— —— (1978) Polyneuropathy, facts and fancies. In: *Contemporary Clinical Neurophysiology*. Edited by W. A. Cobb and H. van Duijn. *Journal of Electroencephalography and Clinical Electrophysiology*, Suppl. 34, pp. 373-383.

BUCHTHAL, F. and ROSENFALCK, A. (1966) Evoked action potentials and conduction velocity in human sensory nerves. *Brain Research, Amsterdam*, **3**, 1-122.

—— —— (1971) Sensory potentials in polyneuropathy. *Brain*, **94**, 241-262.

—— —— and BEHSE, F. (1975) Sensory potentials of normal and diseased nerves. In: *Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas, and E. H. Lambert. Philadelphia: W B. Saunders, Vol. 1, pp. 442-464.

CARUSO, U., LABIANCA, O. and FERRANNINI, E. (1973) Effect of ischæmia on sensory potentials of normal subjects of different ages. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 455-466.

CONN, D. L. and DYCK, P. J. (1975) Angiopathic neuropathy in connective tissue diseases. In: *Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas and E. H. Lambert. Philadelphia: W. B. Saunders, Vol. 2, pp. 1150-1165.

DYCK, P. J. and HOPKINS, A. P. (1972) Electron microscopic observations on degeneration and regeneration of unmyelinated fibres. *Brain*, **95**, 223-234.

GILLIATT, R. W. (1973) Recent advances in the pathophysiology of nerve conduction. In: *New Developments in Electromyography and Clinical Neurophysiology*. Edited by J. E. Desmedt. Basel: Karger, Vol. 2, pp. 2-18.

MCLEOD, J. G. (1975) Carcinomatous neuropathy. In: *Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas and E. H. Lambert. Philadelphia: W. B. Saunders, Vol. 2, pp. 1301-1311.

NIELSEN, V. K. and KARDEL, T. (1974) Decremental conduction in normal human nerves subjected to ischemia? *Acta Physiologica Scandinavica*, **92**, 249-262.

RIDLEY, A. (1975) Porphyric neuropathy. In: *Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas and E. H. Lambert. Philadelphia: W. B. Saunders, Vol. 2, pp. 942-954.

SHARMA, A. K. and THOMAS, P. K. (1974) Peripheral nerve structure and function in experimental diabetes. *Journal of the Neurological Sciences*, **23**, 1-15.

—— —— and BAKER, R. W. R. (1976) Peripheral nerve abnormalities related to galactose administration in rats. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 794-802.

—— —— and DE MOLINA, A. F. (1977) Peripheral nerve fibre size in experimental diabetes. *Diabetes*, **26**, 689-692.

THOMAS, P. K. (1971) The morphological basis for alterations in nerve conduction in peripheral neuropathy. *Proceedings of the Royal Society of Medicine*, **64**, 295-298.

VIZOSO, A. D. and YOUNG, J. Z. (1948) Internodal length and fibre diameter in developing and regenerating nerves. *Journal of Anatomy*, **82**, 110-134.

(*Received January 24, 1978*)

Brain (1978), **101**, 495–511

FACTORS INFLUENCING THE RISK OF MULTIPLE SCLEROSIS DEVELOPING IN PATIENTS WITH OPTIC NEURITIS

by D. A. S. COMPSTON, J. R. BATCHELOR, C. J. EARL *and*
W. I. MCDONALD

(*From the McIndoe Memorial Research Unit, East Grinstead, Moorfields Eye Hospital and the Institute of Neurology, Queen Square*)

INTRODUCTION

THE clinical syndrome of optic or retrobulbar neuritis (ON) is easily recognized in the typical case. After the exclusion of specific causes there remains a sizeable group of patients in whom the ætiology can not be identified (McDonald, 1977). Some of this latter group develop multiple sclerosis (MS) but the fact that after lengthy follow-up some patients do not have further neurological episodes suggests that isolated optic neuritis is more than one disease.

Optic Neuritis and Multiple Sclerosis

The statistics which relate optic neuritis to MS are complex. Some facts are well established: approximately 50 per cent of MS patients have a clinical episode of optic neuritis at some time during the course of their disease (McAlpine, Compston and Lumsden, 1955). Many of the remainder have ophthalmoscopic evidence of damage to the optic nerve and there is electrophysiological evidence of past optic neuritis in 90 per cent of clinically definite MS cases (Halliday, McDonald and Mushin, 1973). All of Lumsden's (1970) 36 unselected necropsies on MS patients showed optic nerve demyelination. Except in Japanese studies optic neuritis is the presenting symptom in approximately 20 per cent of cases (Leibowitz and Alter, 1973).

The risk of MS developing later in patients with isolated optic neuritis is however less certain: the published incidence varies between 85 per cent (Lynn, 1959) and 13 per cent (Kurland, Auth, Beebe, Kurtzke, Lessell, Nagler and Nefzger, 1963). Several factors may contribute to these differences. First, diagnostic criteria for MS and optic neuritis, and the mean length of follow-up, vary between different studies. Bradley and Whitty (1968) found that cases developing MS after optic neuritis had declared themselves within four years, whereas McAlpine, Lumsden and Acheson (1965) concluded 'The longer the period of observation the higher will be the percentage of cases of retrobulbar neuritis which develop signs of MS'. Since therefore the rate at which patients develop MS is unpredictable a comparison of the mean duration of follow-up between studies may not be useful. Secondly, the methods of analysis vary in different investigations. In most, the proportion of cases developing MS has been determined on the basis of the *subsequent* course. However, Nikoskelainen and Riekkinen (1974) also included patients who, when first seen with optic neuritis, had disseminated neurological signs or a history of past neurological symptoms. In the most recent study from Belfast, Hutchinson (1976) predicted on the basis of an actuarial analysis that 78 per cent of patients presenting with optic neuritis will have developed MS after fifteen years.

Finally, the lower proportion of cases of optic neuritis developing MS in all series reported from the United States, compared with studies from Europe, suggests that there may be real differences in the risk of developing MS and that some of these differences may have a geographical basis.

There have been a number of attempts to identify factors which might help to determine the risk of MS developing in the individual patient. Taub and Rucker (1954) investigated the effect of age of onset and found that the risk was marginally increased in those over the age of 20 years, when compared with younger patients. The effect on prognosis of bilateral as opposed to unilateral attacks was studied by Hierons and Lyle (1959). They found no suggestion that bilateral involvement carried a greater risk, irrespective of whether the two eyes were affected simultaneously or sequentially. They did not study recurrent unilateral cases. A number of investigators have noted a slight increase in the attack rate of optic neuritis in the spring and early summer but this seasonal variation has not hitherto proved to be of prognostic value (Taub and Rucker, 1954; Bradley and Whitty, 1967; Hutchinson, 1976).

Genetic predisposition to multiple sclerosis has not previously been investigated as a risk factor in patients with optic neuritis. The observation that the proportion of affected first degree relatives of MS patients is twenty times higher than expected (McAlpine *et al.*, 1965) has led to attempts to identify markers of genetic susceptibility to the disease. Until recently such investigations have been unsuccessful. However, the recent discovery of an association between certain tissue types and MS raises the possibility that tissue typing, at the time of the first neurological episode, might be useful in identifying those patients likely to develop disseminated lesions later. We have explored this possibility in patients presenting with isolated optic neuritis.

In order to understand our approach to the present investigation it will be helpful to review the current state of knowledge of the major histocompatibility system in man and its relationship to MS.

The Human Leucocyte Antigen System (HLA)

Tissue compatibility is now known to be genetically determined. As in all genetic systems it is the gene products—in this case the HLA antigens—which confer specificity. The HLA antigens are coded for by genes occurring at four sites or loci on the sixth chromosome. There is one locus each for the HLA-A, -B, -C and -D genes (Svejgaard, Hauge, Jersild, Platz, Ryder, Staub Nielson and Thomsen, 1975). There are many alternative gene forms or alleles for each locus. Since the cells of each individual have paired chromosomes they will express only two antigens coded for at each of these four loci. Other genes are found in the same region and attention has recently been concentrated on a group of antigens which are mainly expressed on peripheral blood B-lymphocytes. These antigens are of interest because the genes coding for them are thought to be analogous to genes in mice which are involved in the control of the immune response (Svejgaard *et al.*, 1975). The murine antigens have been called immune response associated (Ia) and the human, Ia-like, antigens. The HLA-A, -B and -C antigens are detected by serological tests on unfractionated peripheral blood lymphocytes (60–80 per cent T-lymphocytes) whereas the Ia-like antigens are detected by similar tests on purified peripheral blood B-lymphocytes. The detection of HLA-D antigens is more difficult and depends on techniques involving cellular interaction. The definition of some antigens is still provisional and these are identified by the suffix 'w', for example, HLA-Dw2. Recently it has been shown that the Ia-like and the HLA-Dw antigens are very closely related and may indeed be identical, despite the fact that they are detected by different techniques. Since the evidence is conflicting the WHO Committee on HLA nomenclature has decided to call the Ia-like antigens *HLA-D Related w* (HLA-DRw) antigens (*Histocompatibility Testing, 1977*).

In addition to these internationally accepted antigens a number of individual laboratories have defined Ia-like antigens. Many of these are known to be equivalent to WHO-assigned HLA-DRw antigens, but in other cases, the relationship is still uncertain.

HLA and Multiple Sclerosis

MS was originally shown to be associated with the presence of HLA-A3 and HLA-B7 (Jersild, Svejgaard and Fog, 1972) but the association is weak. It is now thought that these associations are secondary and that an allele at an adjacent locus confers susceptibility to the disease. In many genetic systems an association between particular alleles does not usually occur in randomly mating populations. However in the HLA system there is a tendency for certain alleles (for example, HLA-A3 and -B7) to occur together more frequently than would be expected by chance alone. The biological importance of this phenomenon, known as *linkage disequilibrium*, has been discussed by McDevitt and Bodmer (1974). In relation to MS, the practical problem is to distinguish between the locus which codes for the allele responsible for susceptibility and the loci which code for alleles showing secondary associations due to linkage disequilibrium. The allele showing the highest association is the best candidate for the role of susceptibility gene.

HLA-D antigens were therefore studied and Jersild, Hansen, Svejgaard, Fog, Thomsen and Dupont (1973) demonstrated a stronger association between MS and HLA-Dw2 (original local name Ld7a). The development of relatively convenient and reliable techniques for detecting HLA-DRw antigens has stimulated the search for associations between these antigens and MS. The disease has now been shown to be most closely associated with three locally defined Ia-like antigens —Ag7a (Winchester, Ebers, Fu, Espinosa, Zabriskie and Kunkel, 1975), B group 4 (Terasaki, Park, Opelz and Ting, 1976) and BT 101 (Compston, Batchelor and McDonald, 1976)—and also with HLA-DRw2 (*Histocompatibility Testing, 1977*). In our own series of 156 MS cases BT 101 was present in 79 per cent compared with a frequency of 35 per cent in 85 controls. These HLA-DRw antigen associations with MS have now been confirmed in patients of Northern European stock, in Europe, Australia and North America (*Histocompatibility Testing, 1977*). By contrast, in Jordanian Arabs (Kurdi, Ayesh, Abdallat, Maayta, McDonald, Compston and Batchelor, 1977) and in Italians (*Histocompatibility Testing, 1977*) MS has been found to associate with a specifically different allele, HLA-DRw4.

The question we have tried to answer in this study is whether HLA typing provides a useful guide to the risk of development of MS. Arnason, Fuller, Lehrich and Wray (1974) showed that HLA-A3 was present in a higher proportion of patients with MS than in patients with optic neuritis who had not developed MS during follow-up. The present investigation was designed to assess the prognostic significance of the presence of the antigen BT 101. We also assessed the importance of recurrent or bilateral episodes and the season of onset of optic neuritis.

PATIENTS

The patients in this study had all attended the Physicians' Clinic at Moorfields Eye Hospital, City Road or High Holborn, during the past twenty-three years. They were identified by reviewing all the accessible notes. All available patients in whom a clinical diagnosis of optic neuritis had been made and in whom there was no record of neurological symptoms preceding the episode of visual impairment or signs at the time of presentation were asked to reattend the Clinic. As in our previous investigations, optic neuritis was diagnosed in patients presenting with the rapid onset of visual loss, usually accompanied by ocular pain on movement, in whom there was a reduction in visual acuity, with a central field defect, either with or without a swollen disc (Earl and Martin, 1967; Gould, Bird, Leaver and McDonald, 1977). Patients were excluded if they had a retinal lesion or if there was evidence of a condition other than MS which might cause an optic nerve lesion—for example, gross paranasal sinus disease, blood pressure over 180/110 mmHg or hypertensive retinal vascular disease, diabetes, a history of amaurosis fugax, rheumatic valvular heart disease, a family history of optic nerve disease, heavy tobacco or alcohol consumption, dietary deficiency, Vitamin B12 deficiency, regular use of drugs known to cause optic atrophy, hypercholesterolæmia, syphilis, long-standing visual loss from other causes, patients with a clinical picture suggestive of ischæmic optic neuropathy (Boghen and Glazer, 1975), patients who were not aged between 10 and 50 years at the onset of symptoms and patients in whom the symptoms developed outside Europe, or who were not Caucasian.

One hundred and sixty-four patients were seen in the Clinic between August 1976 and August 1977. Details of their original episode of visual impairment were recorded and enquiry made into any symptoms preceding this and into any illness since the episode of optic neuritis. The date of the first attack of optic neuritis, which was not always the attack which led to the patient's attendance at Moorfields, was obtained where possible from the hospital notes but in a minority of cases the patient's memory was relied upon. The period of follow-up was taken as the time from the onset of the original attack to the time of reassessment or in patients developing MS to the time of development of neurological episodes outside the visual system. A neurological examination was performed on all patients and 10 ml of peripheral blood was taken for HLA typing.

Eighteen patients who failed to fulfil the above criteria were excluded. Using the criteria of McDonald and Halliday (1977) the remaining 146 patients were classified at reassessment as having developed clinically definite, early probable or latent MS (ON/MS) or as having had optic neuritis only (ON-only). Recurrent or bilateral optic neuritis was diagnosed only when there was a clear history of new visual symptoms not attributable to the initial lesion. Patients in whom abnormal physical signs were found in both eyes were classified according to their history. Patients with more than one episode of visual impairment but without other neurological symptoms or signs were classified as having optic neuritis only. Visual evoked potentials had been studied in some of the patients at the time of the initial presentation but the results were not used as a criterion for inclusion in this study. Auditory and spinal evoked potentials were subsequently recorded in a number of patients with clinical evidence of optic neuritis only and those with abnormalities characteristic of demyelination of brain-stem (Robinson and Rudge, 1977) or spinal cord (Small, Matthews and Small, 1978) were classified as latent MS even though the *clinical* signs were restricted to the visual pathways.

IMMUNOLOGY

HLA typing was done using well validated antisera against the HLA-A, -B and -C gene products in both the National Institutes of Health and a local lymphocytotoxicity test (Batchelor, 1973). HLA-DRw typing was done on cell populations enriched for B-lymphocytes by first separating lymphocytes from peripheral blood, anticoagulated with edetic acid (EDTA) by centrifugation over a density gradient of Ficoll-Triosil (metrizoate sodium). The cells were then washed in 5 Mm EDTA and incubated with papain treated sheep red blood cells (SRBCs) at 4° C overnight to form E rosettes. The rosetted T-lymphocytes were separated from the non-rosetted B-lymphocytes, macrophages and monocytes by further centrifugation over Ficoll-Triosil. The 'non-rosetted' cells were harvested, washed and resuspended in McCoy's medium with 0·5 per cent fœtal calf serum. This suspension contained 80–90 per cent B-lymphocytes as judged by the uptake of fluorescent labelled anti-immunoglobulin. T-lymphocytes from the same blood samples were prepared by lysing the SRBCs in the separated E rosettes with 0·85 per cent ammonium chloride, and then washing and resuspending the lymphocytes as described for the B-lymphocytes. This suspension contained 99 per cent T-lymphocytes as judged by 're-rosetting'. T and B enriched cell suspensions from the same peripheral blood sample were always tested in parallel in lymphocytotoxicity tests in which 1 μl of target cell suspension (4×10^6 cells/ml) was incubated with a similar volume of antiserum for one hour at 20° C. The cells were then re-incubated with 5 μl rabbit complement for two hours. 0·4 per cent trypan blue was used to assay cell death. Antisera for HLA-DRw typing were absorbed with pooled platelets (10^{10}/ml) three times at 4° C to remove antibodies directed against HLA-A, -B or -C gene products and all sera used to identify HLA-DRw antigens were shown after absorption to react with B- but not T-lymphocytes from the same blood sample. The cells from all patients were tested against antisera defining many HLA-A, -B, -C and -DRw antigens but in this paper the results are given only for the antigens HLA-B7 and BT101. This Ia-like antigen is equivalent to HLA-DRw2 but also cross-reacts with HLA-DRw1 and some HLA-DRw6 positive cells.

The assignment of the HLA-DRw antigens was made by the WHO Committee after this study was completed and the cells from only a few patients in this study were tested against antisera specific for HLA-DRw2.

STATISTICS

The statistical significance of the results was assessed using the χ^2 test. The relative risk (RR) of MS developing in one group of patients compared with another was calculated according to Svejgaard *et al.* (1975) using the formula

$$\text{RR} = \frac{\text{BT 101-positive ON/MS}}{\text{BT 101-negative ON/MS}} \times \frac{\text{BT 101-negative ON-only}}{\text{BT 101-positive ON-only}}.$$

A value greater than one signifies an increased risk and a value less than one, a decreased risk.

Since the results were inevitably based on a clinical assessment at different stages in each patient's illness and since some patients who at reassessment still had optic neuritis only might later develop MS, an actuarial analysis was made. In this method a prediction is made of the fraction of patients who would remain with optic neuritis only, if all patients had been followed for the same time. This prediction is made for different intervals and a curve drawn. Using the method of Barnes (1965): Fraction with ON/MS at the end of the first interval (0–6 months)

$$= \frac{\text{number of cases developing MS between 0 and 6 months}}{\text{(number of cases entering study)—(half number not followed up for 6 months)}}$$

This fraction with ON/MS is subtracted from one to derive the fraction with optic neuritis only. The new fraction with optic neuritis only is calculated for successive intervals and multiplied by the optic neuritis only fraction for the preceding interval, to obtain the next point on the curve.

RESULTS

Clinical Assessment

One hundred and forty-six patients were reviewed and tissue typed at an interval of one month to twenty-three years after their initial episode of optic neuritis. The mean duration of follow-up was 47·3 months. The results of the clinical analysis are shown in Table 1. Fifty-eight patients (40 per cent) had developed MS (ON/MS);

TABLE 1. CLINICAL ANALYSIS

Total No. patients reassessed		164
Exclusions, non-European Caucasians	2	
,, , symptoms developed outside Europe	2	
,, , episodes preceding optic neuritis	11	
,, , technical	1	
,, , aged > 50 years at onset	2	
		18
Total No. patients in study		146 (100%)
Optic neuritis developing multiple sclerosis (ON/MS)		58 (40%)
clinically definite	36	
early probable or latent	22	
Optic neuritis only (ON-only)		88 (60%)

36 of these were clinically definite and 22 were early probable or latent cases (EPL). Six cases with electrophysiological evidence only of more than one neurological lesion were included in the EPL group. Eighty-eight patients (60 per cent) were classified as optic neuritis only.

Tissue Typing

The results of tissue typing are shown in Table 2. Sixty out of 146 patients (41 per cent) were positive for HLA-B7. This compares with the frequency of 31 per cent in the normal population of South-east England. The higher proportion in our population reflects the inclusion of patients with MS. Thirty-three out of 88 patients (38 per cent) with optic neuritis only were positive for HLA-B7 compared with 27/58 (47 per cent) in the ON/MS group but this difference is not significant ($\chi^2 = 1{\cdot}08$, $P =$ NS). Since the presence of HLA-B7 was not associated with an increased risk of MS in patients with optic neuritis, we did not assess its prognostic value in combination with the other factors that we investigated.

TABLE 2. RESULTS OF TYPING FOR HLA ANTIGENS B7 AND BT 101 IN *ON-ONLY* AND *ON/MS* PATIENTS

	No. studied	*B7*		*BT 101*	
		Positive	*Negative*	*Positive*	*Negative*
All patients	146	60 (41%)	86 (59%)	100 (68%)	46 (32%)
Optic neuritis only	88	33 (38%)	55 (63%)	51 (58%)	37 (42%)
Multiple sclerosis (ON/MS)	58	27 (47%)	31 (53%)	49 (84%)	9 (16%)

⬚ $\chi^2 = 1{\cdot}08$; $P =$ NS; RR $= 1{\cdot}45$. □ $\chi^2 = 11{\cdot}40$; $P < 0{\cdot}001$; RR $= 3{\cdot}95$.

One-hundred out of 146 patients (68 per cent) were positive for BT 101 and this compares with the frequency of 35 per cent of the normal population, again reflecting the inclusion of MS patients. BT 101 was present in 51/88 patients (58 per cent) with optic neuritis only, compared with 49/58 patients (84 per cent) with ON/MS. This difference is significant ($\chi^2 = 11{\cdot}40$, $P < 0{\cdot}001$, RR $= 3{\cdot}95$).

The actuarial curves are shown in fig. 1. At the start of the study (time 0 on the horizontal axis) all patients had optic neuritis only.

Subsequently patients developed MS and the percentage of patients remaining with optic neuritis only (shown on the vertical axis) declined. From the curve based on the whole series it is predicted that 60 per cent of patients will have developed MS by eight years. This figure is in good agreement with the results of previous studies from the UK (Bradley and Whitty, 1968; Bowden, Bowden, Friedmann, Perkin and Rose, 1974). When curves were drawn separately for patients who were BT 101 positive and BT 101 negative, there was a difference in the predicted risk of developing MS which was evident within the first year and became more striking as time went by. The observed occurrence of MS in the

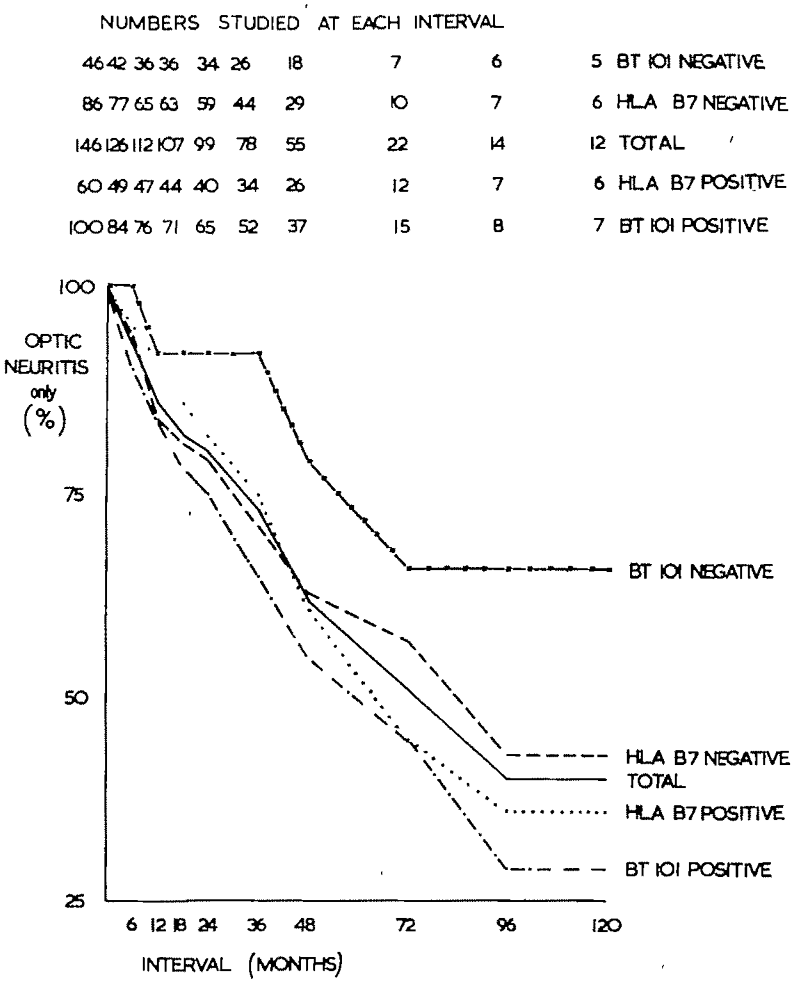


FIG. 1. Actuarial curves showing the percentage of patients with optic neuritis only after different intervals of follow-up. Curves are drawn for patients in five groups: BT 101 negative, HLA-B7 negative, all patients (total), HLA-B7 positive, BT 101 positive. The numbers of patients on whom the calculations are based at each point are shown above the curves.

BT 101 negative group was 9/46 (20 per cent) and the incidence at eight years predicted from the actuarial curve was 34 per cent. This contrasts with the observed incidence of 49/100 cases and the predicted value of 73 per cent at eight years, in the BT 101 positive cases. The significance of the sudden drop in the percentage of cases with optic neuritis only between thirty-six and seventy-two months in the BT 101 negative group is uncertain in view of the small number of cases on which this part of the curve is based.

It is clear that patients with optic neuritis who are BT 101 positive have a significantly greater risk of developing MS than those who are BT 101 negative.

TABLE 3. NUMBER OF CASES PRESENTING IN EACH MONTH OF THE YEAR

	Total	*ON-only BT 101 positive*	*ON-only BT 101 negative*	*ON/MS BT 101 positive*	*ON/MS BT 101 negative*
April	8	3	3	2	—
May	15	13	1	—	1
June	19	5	9	4	1
July	17	8	—	8	1
August	9	4	2	2	1
September	10	2	4	3	1
October	12	4	2	5	1
November	14	4	3	7	—
December	7	—	3	4	—
January	11	2	4	4	1
February	13	4	3	6	—
March	9	2	3	3	1
Total	144	51	37	48	8

Season of Onset

The month of onset of the initial episode of optic neuritis was obtained in 144 patients. Table 3 shows the numbers of optic neuritis only and ON/MS cases presenting in each month. These two clinical groups are further divided into BT 101 positive and negative cases, making four groups in all. For the analysis of the relation between season of onset and prognosis the patients were grouped together as 'summer onset' (April to September inclusive) and 'winter onset' (October to March). Sixty-six out of 144 patients (46 per cent) developed their initial optic neuritis in the winter compared with 78/144 (54 per cent) in the summer. There was a peak within the summer group of cases presenting in May to July which has been noticed in previous studies (*see* Introduction). Table 4 shows that

TABLE 4. SEASON OF ONSET OF OPTIC NEURITIS IN *ON-ONLY* AND *ON/MS* PATIENTS, EACH DIVIDED INTO BT 101 POSITIVE AND NEGATIVE GROUPS

	Number studied	*Winter onset (Oct–March)*	*Summer onset (Apr–Sept)*
All patients	144	66 (46%)	78 (54%)
BT 101-negative ON-only	37	18 (49%)	19 (51%)
BT 101-negative ON/MS	8	3 (38%)	5 (63%)
Total BT 101-negative	45	21 (47%)	24 (53%)
$\chi^2 = 0{\cdot}33$. $P =$ NS. RR $= 0{\cdot}63$.			
BT 101-positive ON-only	51	16 (31%)	35 (69%)
BT 101-positive ON/MS	48	29 (60%)	19 (40%)
Total BT 101-positive	99	45 (45%)	54 (55%)
$\chi^2 = 8{\cdot}41$. $P < 0{\cdot}001$. RR $= 3{\cdot}34$.			

for patients who were BT 101 negative there was no difference in prognosis between patients with winter and summer onset. In contrast patients who were BT 101 positive and who suffered from an attack of optic neuritis in the winter were more likely to develop MS (29/48, 60 per cent) than BT 101 positive patients who had their first attack in the summer (19/48, 40 per cent). The reverse was found in optic neuritis only patients with BT 101 of whom 16/51 (31 per cent) presented in the winter compared with 35/51 (69 per cent) who presented in the summer. This difference is significant ($\chi^2 = 8{\cdot}41$, $P < 0{\cdot}01$, RR $= 3{\cdot}34$).

Bilateral Attacks

There were 140 patients in whom a good history of the number of discrete episodes of visual impairment could be obtained (85 ON-only, 55 ON/MS) and of these 43 (31 per cent) had had more than a single unilateral episode. (Table 5). In those who developed MS the recurrent attacks of optic neuritis preceded historical evidence of demyelination outside the visual system. The 43 patients have been grouped together for analysis irrespective of whether their attacks were recurrent unilateral (10) bilateral and simultaneous (3) bilateral and sequential (24) or both unilateral recurrent and bilateral (6). Sixteen out of 85 patients (19 per cent) with optic neuritis only had had recurrent attacks compared with 27/55 patients (49 per cent) who had developed MS. This difference is significant ($\chi^2 = 14{\cdot}38$. $P < 0{\cdot}001$. RR $= 4{\cdot}16$). The 140 patients in whom the number of episodes of visual impairment was known have been divided into a group with and a group without BT 101 and an analysis of the significance of recurrent episodes on prognosis has been made. In the group who were positive for BT 101 the prognostic significance

TABLE 5. NUMBER OF CASES WITH UNILATERAL OR RECURRENT *ON* IN *ON-ONLY* AND *ON/MS* PATIENTS, EACH DIVIDED INTO BT 101 POSITIVE AND NEGATIVE GROUPS.

	Unilateral	*Recurrent*	*Total*
All patients	97 (69%)	43 (31%)	140
ON-only	69 (81%)	16 (19%)	85
ON-MS	28 (51%)	27 (49%)	55
	$\chi^2 = 14{\cdot}38$: $P < 0{\cdot}001$: RR $= 4{\cdot}16$.		
BT 101-positive ON-only	43 (90%)	5 (10%)	48
BT 101-positive ON/MS	25 (53%)	22 (47%)	47
Total	68 (72%)	27 (28%)	95
	$\chi^2 = 15{\cdot}46$: $P < 0{\cdot}001$: RR $= 7{\cdot}57$.		
BT 101 negative ON-only	26 (70%)	11 (30%)	37
BT 101 negative ON/MS	3 (37%)	5 (63%)	8
Total	29 (64%)	16 (36%)	45
	$\chi^2 = 3{\cdot}08$: $P = \text{NS}$: RR $= 3{\cdot}94$.		

of recurrent attacks is even more marked. Twenty-two out of 47 patients (47 per cent) developing MS had recurrent attacks compared with 5/48 ON only patients (10 per cent: $\chi^2 = 15{\cdot}46$. $P < 0{\cdot}001$. RR = 7·57). Although a similar trend was observed in the BT 101 negative group in that 5/8 patients developing MS had recurrent attacks compared with 11/37 optic neuritis only patients, the numbers are small and the difference is not significant ($\chi^2 = 3{\cdot}08$, P = NS. RR = 3·94).

Combination of Risk Factors

Actuarial curves showing the prognosis of patients who had all three risk factors (that is, BT 101, winter onset of optic neuritis and recurrent episodes) compared with those who had none of them, or combinations of only two, are not shown since the numbers are small: but it is striking that of the 14 patients who had all three factors 12 have developed MS. If these 14 patients are compared with the 126 remaining patients who did not have all three factors and of whom 43 (34 per cent) have developed MS, the difference is highly significant ($\chi^2 = 15{\cdot}32$. $P < 0{\cdot}001$. RR = 11·58).

DISCUSSION

In this study we have identified three factors which are significantly associated with the development of MS after optic neuritis: the presence of the histocompatibility antigen BT 101 (equivalent to HLA-DRw2), recurrence of attacks of optic neuritis and the season of onset of the initial attack. The results will be discussed in terms of the risk to an individual with optic neuritis and in terms of the relationship of optic neuritis to MS in general.

None of the risk factors which has been identified is specific to ON/MS patients and thus does not provide an absolute guide to the risk of MS developing in the individual patient with optic neuritis.

There is a clear association between the development of MS and the presence of BT 101. By using an actuarial method of analysis it is predicted that 73 per cent of optic neuritis patients with, and 34 per cent without, this antigen will develop MS if they are all followed up for at least eight years. The overall figure of 60 per cent is lower than Hutchinson's (1976) figure of 78 per cent developing MS by fifteen years using an actuarial analysis based on clinical observation alone. This suggests that a further 18 per cent of patients with optic neuritis will develop MS after more than eight years and 3 patients in our study have in fact done so already (not shown on the actuarial curves but included in the Tables). These findings are in contrast to the conclusion of Bradley and Whitty (1968) that cases developing MS after optic neuritis declared themselves within four years. It is in agreement with the view of McAlpine *et al.* (1965) that the longer the period of follow-up, the higher the proportion of patients who develop multiple sclerosis.

The increased frequency of MS in cases of recurrent optic neuritis has an important clinical implication. Our results suggest that in the clinical classification of MS it is appropriate to regard recurrent attacks of optic neuritis as separate events, carrying the same significance as episodes of demyelination occurring elsewhere in the central nervous system in a patient with a previous attack of optic neuritis.

The application of the risk factors to the individual patient can thus only add to the suspicion that a patient will develop MS after optic neuritis. We now give a more guarded prognosis to any patient who has had more than one attack of optic neuritis, who is positive for BT 101, and who presented with optic neuritis in the winter.

The ætiology of optic neuritis in those cases in which specific causes have been excluded is unknown. The fact that some patients with optic neuritis subsequently develop MS while others do not, even after prolonged follow-up, suggests that optic neuritis represents more than one disease. Epidemiological surveys of the prevalence rate of multiple sclerosis in migrating populations of one ethnic group provides compelling evidence that an environmental agent is involved in the ætiology of the disease (Dean, 1967; Leibowitz and Alter, 1973). The seasonal variation in the attack rate of optic neuritis suggests that this condition is also caused by environmental agents. The different rate at which MS develops after optic neuritis in BT 101 positive and BT 101 negative cases provides evidence that a genetic factor is also involved. Considering all the evidence from the present investigation together, we conclude that there are at least two forms of optic neuritis, each having different ætiologies, and that the subsequent development of MS is due to a specific interaction between one of the environmental agents causing optic neuritis and the genetically susceptible host. We suggest that MS does not develop unless both factors are present. There is a tendency for the 'benign' summer agent not to produce MS even in the susceptible host, and for neither of the putative agents to produce MS in the genetically non-susceptible host. The postulated environmental agent causing MS might be identified by comparing exposure to viral infection in BT 101 positive patients who have the first attack of optic neuritis during the winter with exposure in genetically matched controls studied at the same time. In this way comparison of patients with inappropriate controls who may have been exposed to different environmental agents or who may never have been at risk of developing MS, whatever environmental events have occurred, would be avoided.

Although Sibley and Foley (1965) noted a seasonal variation in attacks of MS, with a significant increase in July to October, there was no significant seasonal variation in the *onset* of MS. It remains to be determined whether MS patients with modes of presentation other than optic neuritis, classified on the basis of tissue type, also show a seasonal variation in onset. It is possible that different presentations of MS may be due to different causes or be the result of a different combination of events.

Although the results of the present investigation provide further evidence that there is a genetic factor leading to susceptibility to MS, and that this factor operates through specific interaction with an environmental agent, the nature of the interaction remains obscure. Several lines of evidence suggest that an immunological mechanism is involved. First, the closest genetic marker of MS susceptibility yet identified is an Ia-like (HLA-DRw) antigen. Secondly, antibody of specific electrophoretic mobility (oligoclonal IgG) is found in the spinal fluid of over 90 per cent of MS patients (Link and Müller, 1971; Thompson, E. J., Kaufmann, P., Rudge, P. and McDonald, W. I., unpublished data). Thirdly, antibody secreting cells have been demonstrated in the vicinity of MS plaques (Wright and Prineas, 1977; Esiri, 1977). Fourthly, an increase in the titre of humoral antibodies in blood and CSF to a variety of viruses has been widely reported (*see* Fraser, 1975) but the lack of specificity of these observations to MS makes them difficult to interpret. Finally, the balance of evidence suggests that cellular immunity is depressed in MS, although the details of the abnormalities remain poorly defined (Knight, 1977).

While there is thus good evidence that abnormalities of the immune system exist in MS, their mode of operation is unknown. A number of diseases are known to have an autoimmune basis (for example, chronic active hepatitis, myasthenia gravis). These diseases have been shown to be associated with HLA-B8, and DRw3 (*Histocompatibility Testing, 1977*). The fact that MS is not associated with these antigens suggests that its exact pathogenesis is different. Furthermore, although in laboratory animals sensitization of immune competent cells to CNS antigens results in autoimmune demyelination (experimental allergic encephalomyelitis), attempts to demonstrate evidence for a similar mechanism in MS have been unsuccessful (Caspary, 1977).

The existence of additional immunopathological mechanisms is well established in experimental animals. In mice, the H2 system (murine equivalent of the human HLA system) is intimately involved in the recognition of foreign antigens (Miller, Vadas, Whitelaw and Gamble, 1976), in their handling (Erb and Feldmann, 1974), and in their elimination (Shearer, 1974), including viruses such as lymphocytic choriomeningitis virus (Doherty and Zinkernagel, 1975). Other evidence suggests that antigens coded for at each locus may contribute in complementary ways to this handling (Munro and Bright, 1976). That similar processes may occur in man is suggested by the recent observation that the cellular immune response to vaccinia virus (de Vries, Kreeftenberg, Loggen and Van Rood, 1977) and cell-mediated lysis of influenza-virus-infected human target cells (McMichael, Ting, Zweerink and Askonas, 1977) is HLA restricted.

It is possible that the possession of the genetically determined antigens HLA-B7 -Dw2 and in particular -DRw2 might confer on an individual a disadvantage in the ability to handle infection by the MS causative agent or group of agents. Subsequent damage to the central nervous system would result from the agent (possibly a virus) persisting and allowing damaging immunological processes to develop. Although there are a number of reports of virus recovery from brain and other tissues from MS patients (ter Meulen, Iwasaki, Koprowski, Käckell and

Müller, 1972; Thorne and Dermott, 1976; Prasad, Broome, Pertschuk, Gupta and Cook, 1977; Warren, Gilden, Brown, Devlin, Wroblewska, Subak-Sharpe and Koprowski, 1977) no single organism has been consistently isolated (Johnson, 1977; Woyciechowska, Madden and Sever, 1977) and at present the question of persistent infection by a pathogenic organism in MS is unresolved.

Finally, there is the general question as to why an antigen such as DRw2 which may confer susceptibility to a disease persists in the Caucasian population. Presumably, as in the case of the sickle cell trait and malaria, there is a balancing advantage to the population concerned, but its nature is completely unknown.

SUMMARY

One-hundred and forty-six patients who had presented with optic neuritis but without evidence of demyelination elsewhere in the nervous system, and in whom no specific cause could be identified, were reassessed clinically between one month and twenty-three years after the onset. Fifty-eight patients (40 per cent) had developed MS. All 146 patients were HLA-typed. Three factors were identified which were significantly associated with the development of MS: positive typing for the HLA antigen BT 101, winter onset of the initial attack of optic neuritis in BT 101-positive patients only, and recurrent attacks of optic neuritis. The application of these results to the individual patient is of limited use. However, recurrent attacks of optic neuritis should be given the same significance in the clinical classification of MS as episodes of demyelination occurring elsewhere in the central nervous system in a patient with a previous attack of optic neuritis. The results suggest that optic neuritis is caused by two different environmental agents or groups of agents and that the agent which is most common in the winter leads to the development of MS in the genetically susceptible individual. The agent more common in the summer is much less likely to cause MS in either susceptible or non-susceptible individuals. The biological role of the HLA system in the handling of foreign antigens is discussed and it is suggested that the presence of the HLA antigens associated with MS confers a specific disadvantage on individuals in the ability to handle infection by the MS causative agent and that this allows damaging immunological processes to develop.

ACKNOWLEDGEMENTS

This work was supported in part by grants from the Medical Research Council and the East Grinstead Research Trust. We thank Mrs. G. Clare, Mrs. J. Hirsch, Mrs. C. Seymour and Mrs. L. Simmons for excellent technical assistance.

Requests for reprints should be addressed to Professor W. Ian McDonald, Institute of Neurology, Queen Square, London, WC1N 3BG.

REFERENCES

ARNASON, B. G. W., FULLER, T. G., LEHRICH, J. R. and WRAY, S. H. (1974) Histocompatibility types and measles antibodies in multiple sclerosis and optic neuritis. *Journal of the Neurological Sciences*, **22**, 419–428.

BARNES, B. A. (1965) Survival date of renal transplant in patients. *Transplantation*, **3**, 812–821.

BATCHELOR, J. R. (1973) In: *Handbook of Experimental Immunology*. Edited by D. M. Weir. Oxford: Blackwell. Vol. 2, 32, 32.1–32.14.

BOGHEN, D. R. and GLAZER, J. S. (1975) Ischæmic optic neuropathy. The clinical profile and natural history. *Brain*, **98**, 689–708.

BOWDEN, A. N., BOWDEN, P. M. A., FRIEDMANN, A. I., PERKIN, G. D. and ROSE, F. C. (1974) A trial of corticotrophin gelatin injection in acute optic neuritis. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 869–873.

BRADLEY, W. R. and WHITTY, C. W. M. (1967) Acute optic neuritis: its clinical features and their relation to prognosis for recovery of vision. *Journal of Neurology, Neurosurgery and Psychiatry*, **30**, 531–538.

—— —— (1968) Acute optic neuritis: prognosis for development of multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **31**, 10–18.

CASPARY, E. A. (1977) Humoral factors involved in immune processes in multiple sclerosis and allergic encephalomyelitis. *British Medical Bulletin*, **33**, 50–53.

COMPSTON, D. A. S., BATCHELOR, J. R. and MCDONALD, W. I. (1976) B-lymphocyte alloantigens associated with multiple sclerosis. *Lancet*, **ii**, 1261–1265.

DEAN, G. (1967) Annual incidence, prevalence and mortality of multiple sclerosis in white South-African-born and in white immigrants to South Africa. *British Medical Journal*, **2**, 724–730.

DOHERTY, P. C. and ZINKERNAGEL, R. M. (1975) A biological role for the major histocompatibility antigens. *Lancet*, **i**, 1406–1409.

EARL, C. J. and MARTIN, B. (1967) Prognosis in optic neuritis related to age. *Lancet*, **i**, 74–76.

ERB, P. and FELDMAN, M. (1974) The role of macrophages in the generation of T-helper cells. II. The genetic control of the macrophage-T-cell interaction for helper cell induction with soluble antigens. *Journal of Experimental Medicine*, **142**, 460–472.

ESIRI, M. M. (1977) Immunoglobulin containing cells in multiple sclerosis plaques. *Lancet*, **ii**, 478–480.

FRASER, K. B. (1975) Population serology. In: *Multiple Sclerosis Research*. Proceedings of a joint conference held by the Medical Research Council and the Multiple Sclerosis Society of Great Britain and Northern Ireland. Edited by A. N. Davison, J. H. Humphrey, L. A. Liversedge, W. I. McDonald and J. S. Porterfield. London: HMSO, Chapter 4, pp. 53–68.

GOULD, F. S., BIRD, A. C., LEAVER, P. K. and MCDONALD, W. I. (1977) Treatment of optic neuritis by retrobulbar injection of triamcinolone. *British Medical Journal*, **1**, 1495–1497.

HALLIDAY, A. M., MCDONALD, W. I. and MUSHIN, J. (1973) Visual evoked response in diagnosis of multiple sclerosis. *British Medical Journal*, **4**, 661–664.

HIERONS, R. and LYLE, T. K. (1959) Bilateral retrobulbar optic neuritis. *Brain*, **82**, 56–67.

Histocompatibility Testing (*1977*) Edited by W. F. Bodmer, J. Bodmer, J. R. Batchelor, H. Festenstein and P. J. Morris. Copenhagen: Munksgaard. In preparation.

Hutchinson, W. M. (1976) Acute optic neuritis and the prognosis for multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 283–289.

Jersild, C., Svejgaard, A. and Fog, T. E. (1972) HL-A antigens and multiple sclerosis. *Lancet*, **i**, 1240–1241.

—— Hansen, G. S., Svejgaard, A., Fog, T. E., Thomsen, M. and Dupont, B. (1973) Histocompatibility determinants in multiple sclerosis with special reference to clinical course. *Lancet*, **ii**, 1221–1225.

Johnson, R. T. (1977) Virological data supporting the viral hypothesis in multiple sclerosis. In: *Multiple Sclerosis Research*. Proceedings of a joint conference held by the Medical Research Council of Great Britain and Northern Ireland. Edited by A. N. Davison, J. H. Humphrey, L. A. Liversedge, W. I. McDonald and J. S. Porterfield. London: HMSO. Chapter 10, pp. 155–177.

Knight, S. C. (1977) Cellular immunity in multiple sclerosis. *British Medical Bulletin*, **33**, 45–49.

Kurdi, A., Ayesh, I., Abdallat, A., Maayta, U., McDonald, W. I., Compston, D. A. S. and Batchelor, J. R. (1977) Different B-lymphocyte alloantigens associated with multiple sclerosis in Arabs and North Europeans. *Lancet*, **i**, 1123–1125.

Kurland, L. T., Auth, T. L., Beebe, G. W., Kurtzke, J. F., Lessell, S., Nagler, B. and Nefzger, M. D. (1963) Studies on the natural history of multiple sclerosis. 2. Progression from optic neuropathy to multiple sclerosis. *Transactions of American Neurological Association*, **88**, 233–235.

Leibowitz, U. and Alter, M. (1973) *Multiple Sclerosis. Clues to its Cause*. Amsterdam: North Holland.

Link, H. and Müller, R. (1971) Immunoglobulins in multiple sclerosis and infections of the nervous system. *Archives of Neurology, Chicago*, **25**, 326–344.

Lumsden, C. E. (1970) The neuropathology of multiple sclerosis. In: *Handbook of Clinical Neurology*. Edited by P. J. Vinken and G. W. Bruyn, Amsterdam: North Holland. Vol. 9, pp. 217–309.

Lynn, B. H. (1959) Retrobulbar neuritis. A survey of the present condition of cases occurring over the last 56 years. *Transactions of the Ophthalmological Society of the United Kingdom*, **79**, 701–716.

McAlpine, D., Compston, N. D. and Lumsden, C. E. (1955) *Multiple Sclerosis*. Edinburgh: Livingstone.

—— Lumsden, C. E. and Acheson, E. D. (1965) *Multiple Sclerosis. A Re-appraisal*. Edinburgh: Livingstone.

McDevitt, H. O. and Bodmer, W. F. (1974) HL-A, immune response genes, and disease. *Lancet*, **i**, 1269–1275.

McDonald, W. I. (1977) Acute optic neuritis. *British Journal of Hospital Medicine*, **18**, 42–48.

—— and Halliday, A. M. (1977) Diagnosis and classification of multiple sclerosis. *British Medical Bulletin*, **33**, 4–8.

McMichael, A. J., Ting, A., Zweerink, H. J. and Askonas, B. A. (1977) HL-A restriction of cell-mediated lysis of influenza virus infected human cells. *Nature, London*, **270**, 524–526.

Meulen, V. ter, Iwasaki, Y., Koprowski, H., Käckell, Y. M. and Müller, D. (1972) Fusion of cultured multiple sclerosis brain cells with indicator cells: Presence of nucleocapsids and virions and isolation of parainfluenza-type virus. *Lancet*, **ii**, 1–5.

MILLER, J. F. A. P., VADAS, M. A., WHITELAW, A. and GAMBLE, J. (1976) Role of major histocompatibility complex gene products in delayed-type hypersensitivity. *Proceedings of the National Academy of Sciences of the USA*, **73**, 2486–2490.

MUNRO, A. and BRIGHT, S. (1976) Products of the major histocompatibility complex and their relationship to the immune response. *Nature, London*, **264**, 145–152.

NIKOSKELAINEN, E. and RIEKKINEN, P. (1974) Optic neuritis—a sign of multiple sclerosis or other diseases of the central nervous system. *Acta Neurological Scandinavica*, **50**, 690–718.

PRASAD, I., BROOME, J. D., PERTSCHUK, L. P., GUPTA, J. and COOK, A. W. (1977) Recovery of paramyxovirus from the jejunum of patients with multiple sclerosis. *Lancet*, **i**, 1117–1119.

ROBINSON, K. and RUDGE, P. (1977) Abnormalities of the auditory evoked potentials in patients with multiple sclerosis. *Brain*, **100**, 19–39.

SHEARER, G. M. (1974) Cell mediated cytotoxicity to trinitrophenyl-modified syngeneic lymphocytes. *European Journal of Immunology*, **4**, 527–533.

SIBLEY, W. A. and FOLEY, J. M. (1965) Infection and immunization in multiple sclerosis. *Annals of the New York Academy of Sciences*, **122**, 457–468.

SMALL, D. G., MATTHEWS, W. B. and SMALL, M. (1978) The cervical somatosensory evoked potential SEP in the diagnosis of Multiple sclerosis. *Journal of the Neurological Sciences*, **35**, 211–224.

SVEJGAARD, A., HAUGE, M., JERSILD, C., PLATZ, P., RYDER, L. P., STAUB NIELSEN, L. and THOMSEN, M. (1975) The HLA system. An introductory survey. *Monographs in Human Genetics*. Edited by L. Beckman and M. Hauge. Basel: Karger. Vol. 7, pp. 1–103.

TAUB, R. G. and RUCKER, T. W. (1954) The relationship of retrobulbar neuritis to multiple sclerosis. *American Journal of Ophthalmology*, **37**, 494–497.

TERASAKI, P. I., PARK, M. S., OPELZ, G. and TING, A. (1976) Multiple sclerosis and high incidence of a B lymphocyte antigen. *Science*, **193**, 1245–1247.

THORNE, H. V. and DERMOTT, E. (1976) Circular and elongated linear forms of measles virus nucleocapsid. *Nature, London*, **264**, 473–474.

VRIES, R. R. P. de., KREEFTENBERG, H. G., LOGGEN, H. G. and VAN ROOD, J. J. (1977) In vitro immune responsiveness to vaccinia virus and HLA. *New England Journal of Medicine*, **297**, 692–696.

WARREN, K. G., GILDEN, D. H., BROWN, S. M., DEVLIN, M., WROBLEWSKA, Z., SUBAK-SHARPE, J. and KOPROWSKI, H. (1977) Isolation of herpes simplex virus from human trigeminal ganglia, including ganglia from one patient with multiple sclerosis. *Lancet*, **ii**, 637–639.

WINCHESTER, R. J., EBERS, G., FU, S. M., ESPINOSA, L., ZABRISKIE, J. and KUNKEL, H. G. (1975) B-cell alloantigen Ag7a in multiple sclerosis. *Lancet*, **ii**, 814.

WOYCIECHOWSKA, J. L., MADDEN, D. L. and SEVER, J. L. (1977) Absence of measles virus antigen in jejunum of multiple sclerosis patients. *Lancet*, **ii**, 1046–1049.

WRIGHT, R. G. and PRINEAS, J. W. (1977) Plasma cells in the nervous system in multiple sclerosis (Abstract). *11th World Congress of Neurology, Amsterdam*. Edited by W. A. der Hartog Jager, G. W. Bruwyn and A. P. J. Heijstee. Amsterdam and Oxford: Excerpta Medica, p. 300.

(*Received February 14, 1978*)

Brain (1978), **101**, 513–541

THE INTRINSIC CONNECTIONS OF THE CORTEX OF AREA 4 OF THE MONKEY[1]

by K. C. GATTER *and* T. P. S. POWELL

(*From the Department of Human Anatomy, South Parks Road, Oxford*)

INTRODUCTION

FOLLOWING the original demonstration that contraction of muscles could be elicited by electrical stimulation of the pericruciate region of the cortex in dogs (Fritsch and Hitzig, 1870) and of the pre- and post-central gyri of monkeys (Ferrier, 1873) several studies were devoted to 'localise the motor function of each cortical point yielding motor responses' (Leyton and Sherrington, 1917). The surprising finding of the earlier workers was that although stimulation of a point on the cortex always resulted in movement of the same part of the body, the details of the response varied according to the time and place of previous stimulation and took the form of either facilitation, deviation or reversal of the initial response. Leyton and Sherrington (1917) considered 'the functional instability of cortical motor points are indicative of the enormous wealth of mutual associations existing between the separable motor cortical points, and those associations must be a characteristic part of the machinery by which the synthetic powers of that cortex are made possible'.

Recent studies which have been done with the purpose of determining in more detail the principles of localization within the motor cortex have used increasingly refined methods of electrical stimulation. These have included single rectangular cathodal or anodal pulses to the surface of the cortex (Liddell and Phillips, 1950, 1952; Hern, Landgren, Phillips and Porter, 1962; Jankowska, Padel and Tanaka, 1975*b*) or intracortical microstimulation (Asanuma and Rosén, 1972; Andersen, Hagan, Phillips and Powell, 1975) but even with these methods there is the possibility of activation of both the corticospinal and intrinsic neurons, and the need for further information about the organization of the cells and their intrinsic connections has been emphasized.

Histological studies of the motor cortex, particularly of material impregnated with the Golgi method (*see* Cajal, 1911; Marin-Padilla, 1969, 1970; Scheibel and Scheibel, 1970) have provided considerable information about the somata, dendritic processes and axonal ramifications of some of the cells and of the predominantly radial arrangement of the fibres in the deeper layers. In recent years fibre degeneration techniques have been used to investigate the intrinsic connections of other areas of the cortex (Spatz, Tigges and Tigges, 1970; Nauta, Butler and Jane, 1973; Fisken, Garey and Powell, 1975; Creutzfeldt, Garey, Kuroda and Wolff, 1977), and in area 17 of the visual cortex of the monkey it was possible to determine the distribution and extent of these connections in terms of the laminæ of the cortex and to make certain correlations with functional observations of the same area (Fisken *et al.*, 1975). The intrinsic connections of area 4 of the monkey have now been studied after the placement of small microelectrode lesions within the cortex. It was hoped that the information obtained would help in the interpretation of electrophysiological studies upon this area and also that a comparison with the findings in area 17, which is so different structurally and functionally, might provide some clues about the factors influencing the pattern of connections within the cortex.

---

[1] Some of the research reported in this and the following paper was presented in an Invited Lecture delivered at the Scientific Meeting which was held on 5 April 1978 to celebrate the Centenary of *Brain*.

MATERIAL AND METHODS

Twelve young adult monkeys were used in this study and all the operations were performed under Nembutal anæsthesia with full aseptic precautions. The precentral gyrus of one hemisphere was exposed and small lesions were made in the cortex of area 4 either with a tungsten microelectrode (Hubel, 1957), or, in a few cases, freehand with a steel needle. In the initial experiments it was found that the degeneration within the cortex was restricted to within a few millimetres of the lesion, and consequently in later experiments several lesions were made in the precentral gyrus but they were always placed sufficiently apart to prevent overlap of the degeneration. Lesions were made in all the topographic subdivisions of area 4 and throughout its anteroposterior and mediolateral extent. The majority of the electrode penetrations were made perpendicular to the surface of the cortex, but a few were made obliquely at approximately 45 degrees to the surface. The electrodes were inserted to a known depth and in most penetrations a current of 10 μA was passed throughout the traverse of the cortex, but in a few cases no current was passed. The position and depth of individual lesions were recorded at the time of operation.

After a survival period of three to four days the animals were again anæsthetized and perfused through the heart with 0·9 per cent saline and 10 per cent formalin. The brains were removed and immersed in the fixative for a further period of several weeks. Blocks containing the pre- and post-central gyri were taken and after soaking in 30 per cent sucrose for seven to ten days were cut at 25 μm on the freezing microtome. Most of the blocks were cut in either the sagittal or coronal plane, but a few were cut tangential to the surface of the cortex. All sections were collected and a 1:20 series was stained with either the Fink-Heimer (1967) or Wiitanen (1969) techniques and examined for the presence of lesions. An alternative series of sections was stained until all the lesions had been found, and then serial sections stained over the extent of individual lesions and the resulting degeneration.

RESULTS

A total of 53 lesions was placed in the cortex of area 4 and of these, 43 have been used, the other 10 being discarded either because of poor impregnation of the sections or because of adjoining incidental damage. To facilitate the description of the results the lesions will be divided into groups according to the depth of the lesion and the laminæ involved. The depth of the lesions will be described in terms of the laminæ, although there is unavoidably some uncertainty because of the well-known difficulty in distinguishing some of the laminæ in area 4; where a lesion has encroached upon the superficial margin of a lamina it has been assumed that it was involved. Both the Fink-Heimer and Wiitanen methods resulted in good impregnation of degenerating terminals and fibres, and the Wiitanen method had the added advantage that the cell bodies were also impregnated so that additional sections stained by the Nissl method were not required. Since the slightest damage to the neocortex, either direct or ischæmic, will result in fibre and terminal degeneration, and because many of our lesions were small with the degeneration localized to within a few millimetres, care was taken to exclude the possibility that the degeneration due to the lesion could be attributed to such incidental damage.

In Nissl sections cut in the sagittal plane or perpendicular to the central sulcus the cortex of area 4 is 3 to 4 mm in thickness and approximately twice that of the somatic sensory area in the adjoining postcentral gyrus. Layer I is almost devoid of neurons and is thicker than in the adjoining cortical areas. Layer II is made up mainly of small pyramids closely packed together and easily demarcated; it is slightly thicker than layer I. In layer III, which consists predominantly of pyramidal cells, the neurons are larger, more widely separated and arranged in columns. In the outer part of this layer the cells are more densely arranged and smaller than in the deeper part. Layer IV, although narrow, can be recognized and forms a lighter band just superficial to the characteristic large Betz cells of this architectonic area. Many of the constituent cells are small, round and pale-staining. Layer V has the large Betz cells near its superficial margin and its constituent neurons are arranged in columns perpendicular to the surface. Although the Betz cells are always near the upper margin of this layer, the depth of them varies so that they form a tortuous line; they are frequently in groups of about 2 to 4 and separated by intervals from adjoining ones. The other pyramidal cells at the level of the Betz cells are also quite large but those more deeply situated in this layer are smaller and distinctly triangular. In layer VI, which merges very gradually with the underlying white matter, the cells have a less pronounced pyramidal shape and are more widely separated. The columnar arrangement of the cells is most prominent on the exposed lateral surface of the gyrus and on the anterior bank of the central sulcus, where their radial arrangement in relation to the curvature of the surface is very striking. In the deep half of the anterior wall of the central sulcus, which contains the representation of the hand, the columnar pattern is not so clear.

In sections stained with the Wiitanen method where there has been only partial suppression of the impregnation of normal fibres there are many features of relevance to the interpretation of the experimental findings. There is a distinct difference in the number and pattern of the fibres superficial and deep to the level of layer IV and the Betz cells. In layers V and VI there is a radial arrangement of the fibres at low magnifications, and at higher magnifications this is seen to be due to narrow bundles of fibres, 3 to 6 fibres in each, passing perpendicularly between and parallel to the rows of cells and separated by approximately 50 μm (fig. 4A). At the level of the Betz cells there is a horizontal plexus of quite coarse fibres and the cells are in the middle of it. Throughout the depth of layer V many similar large fibres pass horizontally for considerable distances, and in parts of the cortex there are concentrations of these into a less distinct plexus near the deep margin of the layer. An occasional large fibre can be traced for several millimetres as it passes obliquely through the depth of both layers V and VI. Superficial to layer IV there are far fewer fibres impregnated and these are more irregularly distributed; many of the radially orientated bundles of fibres seen in the deep layers break up into finer branches which disperse in different directions, but a small number continue in a radial direction into layer III.

In the first group of lesions which were examined in sagittal sections the damage extended through the depth of the cortex and in only two of them did it continue into the underlying white matter, and then for a distance of only 0·5 to 1 mm.

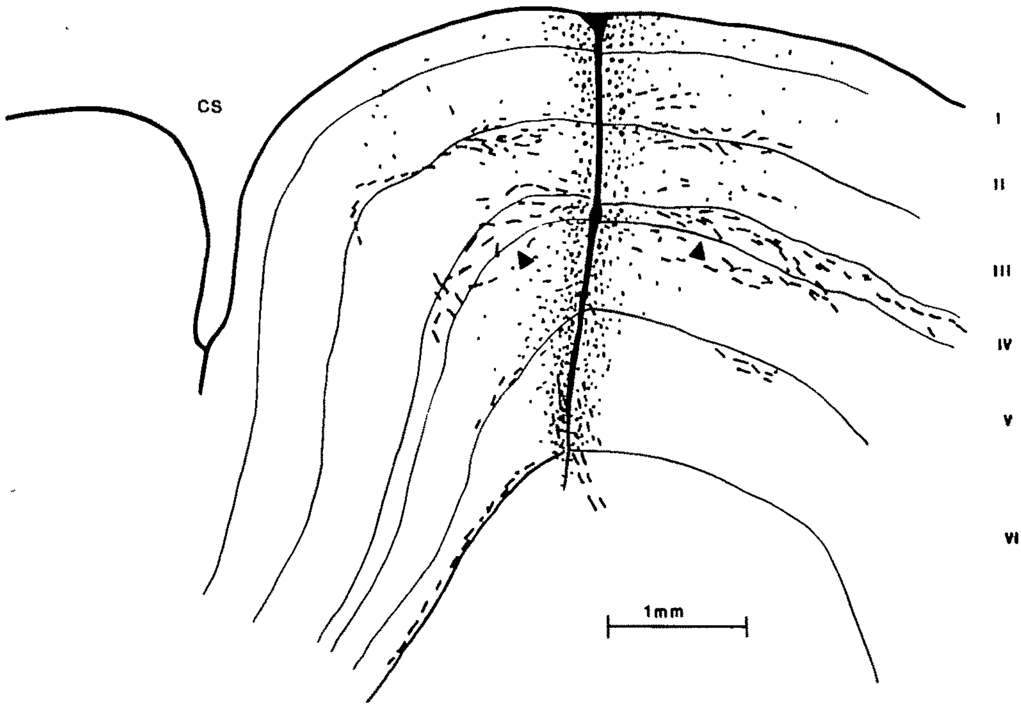


FIG. 1. The fibre and terminal degeneration in a sagittal section resulting from a perpendicular microelectrode lesion through the full depth of the cortex of area 4. In this and subsequent figures the lesion is shown in solid black, the fibre degeneration by short lines and the terminal degeneration by dots. The laminæ of the cortex are indicated by Roman numerals on the right of the figure and Betz cells by solid triangles in the superficial part of layer V. Abbreviations: A = anterior. ASS = anterior subcentral sulcus. CS = central sulcus L = lateral M = medial. P = posterior. Roman numerals I–VI = layers of cortex

As far as can be judged the extent and pattern of the degeneration was the same irrespective of the site involved. A lesion in the lateral part of the precentral gyrus functionally related to the head and just anterior to the central sulcus is typical of this group (figs. 1, 2 and 3). It forms a slit 60 μm wide through the depth of the cortex and barely encroaches upon the underlying white matter. Immediately adjoining it and of uniform density and width throughout the depth of the cortex is a narrow zone of intense finely granulated degeneration 200 to 300 μm in width on each side. There is then a sudden sharp decrease in the degeneration and beyond this the appearance of the fibre and terminal degeneration varies in the different layers. In layer I there is fine degeneration and horizontally disposed fragments gradually diminishing in amount over 1 to 2 mm on each side of the lesion. In all other layers there is a moderate degree of terminal and fibre degeneration over the same distance. Fibre fragments are disposed at all angles, some of which may be traced in continuity for distances of one or more millimetres, especially those disposed horizontally or obliquely in layer V; the size of these fragments varies, some being quite coarse.

At the junction of layers II and III there is degeneration of fine fibres which are arranged horizontally (fig. 4c). More deeply, from the level of layer IV to just below the Betz cells there is another band of horizontal degenerating fibres which are larger than those at the boundary of layers II and III. They extend for a short

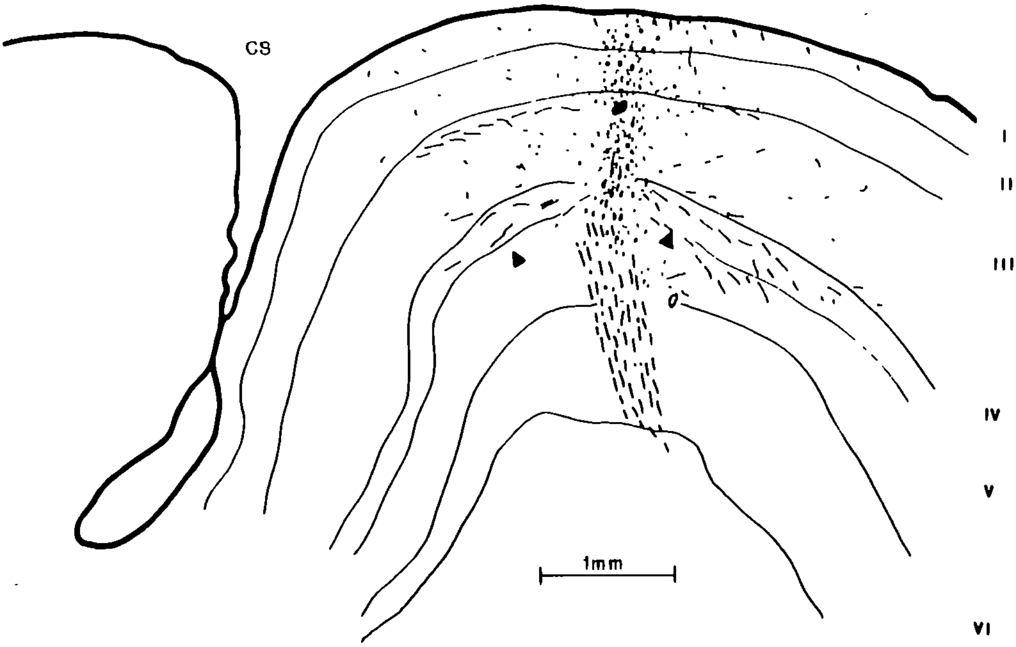


FIG. 2. Fibre and terminal degeneration on a section adjoining that in fig. 1 and in which only a small part of the lesion is still present. The degenerating efferent fibres passing through layers V and VI are orientated parallel to each other and restricted to the width of the lesion and dense degeneration. For abbreviations *see* fig. 1

distance further than the degeneration in other layers and have a close relationship to the Betz cells (figs. 5B and C, 6A and B) and to the large pyramidal cells in the deep part of layer III. In the deeper parts of layer V the fibre fragments are again mainly arranged horizontally. Apart from these plexi of horizontally degenerating fibres the intensity of the terminal and fibre degeneration appears to be the same throughout the depth of the cortex. On the sections containing the electrode track the degeneration extends further anteriorly (2·75 mm) than posteriorly (1·75 mm), but on adjoining sections this asymmetry is less marked and the extent of the degeneration diminishes. On sections adjacent to the track a new feature is the presence of vertically disposed degenerating fibres extending from layer IV through to the white matter (fig. 4B). They form a conspicuous band at precisely the anteroposterior level of the lesion and of the same width as the zone of dense degeneration, approximately 500 to 600 μm wide. On sections progressively further from the lesion the degeneration decreases and it is difficult to be certain of its precise extent in the mediolateral dimension.

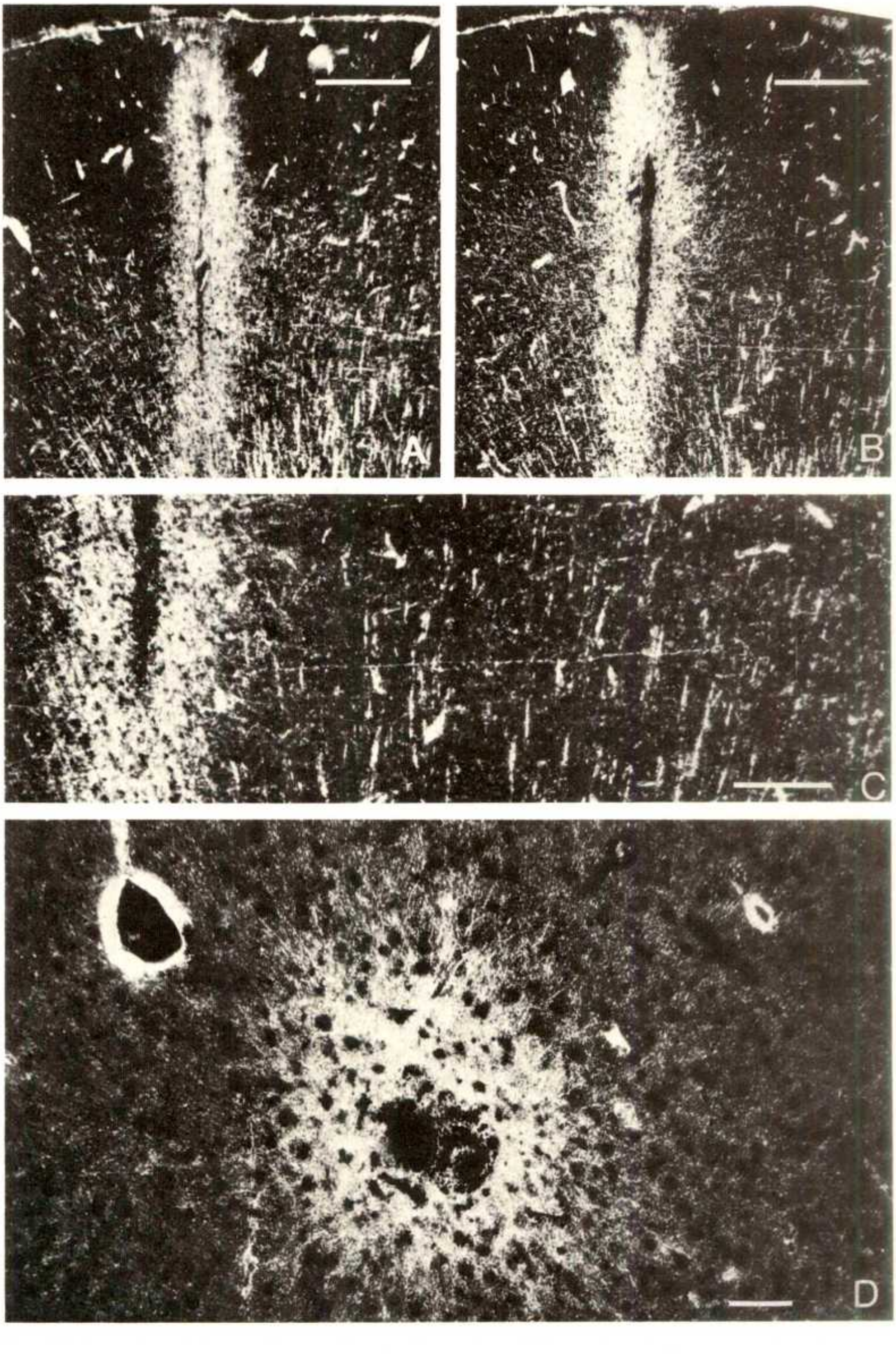
In the two experiments in which the tip of the electrode penetrated the white matter for 0·5 to 1·0 mm there was no appreciable difference in the intensity and distribution of the degeneration within the cortex, no doubt due to the minimal involvement of afferent fibres.

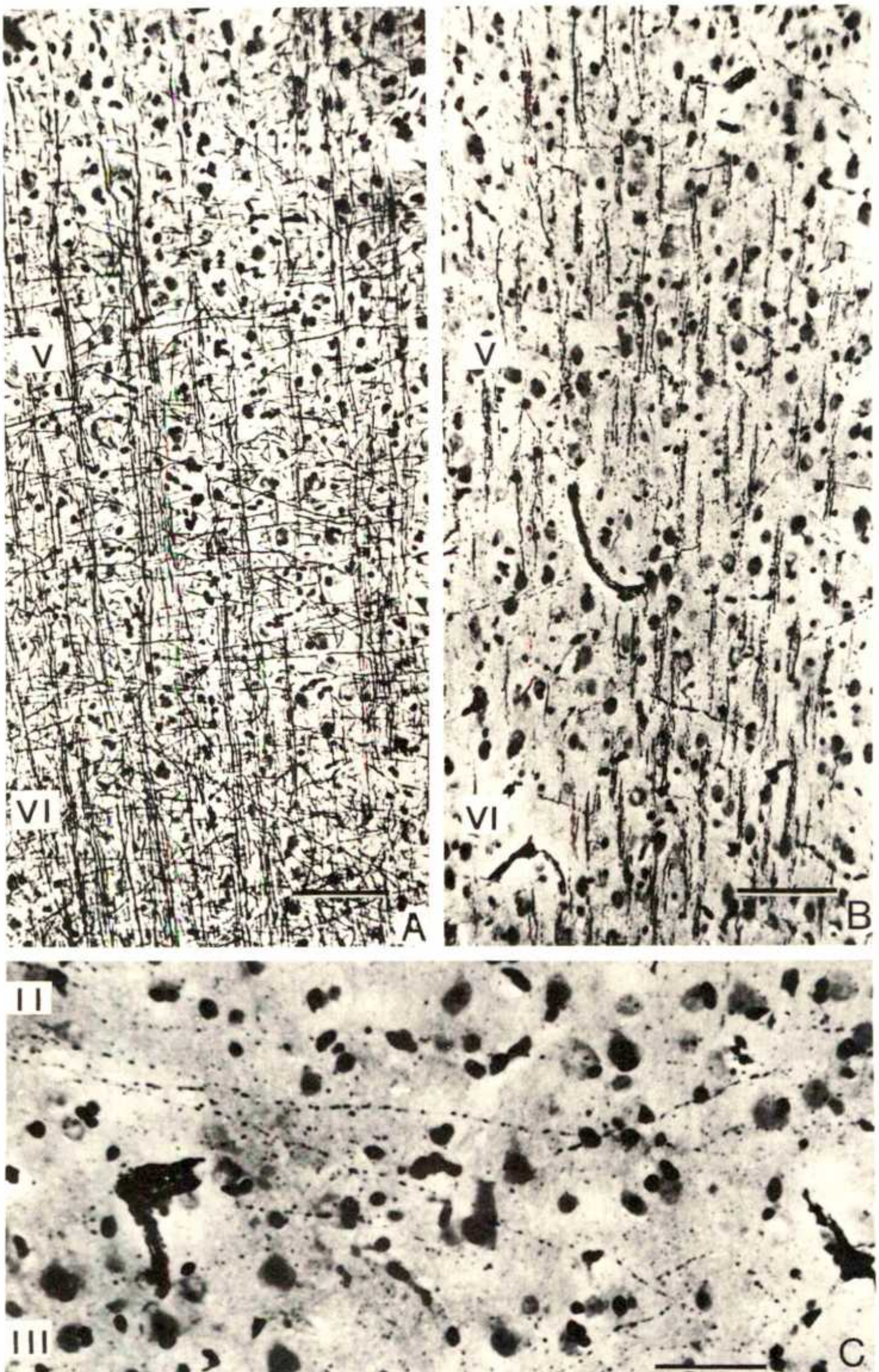
Apart from an occasional obliquely disposed degenerating fibre in the deeper layers, some of which can be traced into the white matter, there is no separate focus of appreciable degeneration in area 4 but definite degeneration can be seen in restricted bands in areas 1 and 2 of the somatic sensory cortex at the level of the lesion. The cortex of area 6 has not been systematically studied for projections from area 4.

In one of the penetrations made obliquely to the surface the track reached to just below the Betz cells close to the bank of the central sulcus (fig. 7A). Superficial and deep to the track there is dense granular degeneration for a few hundred microns and there is a moderate degree of fibre and terminal degeneration within a few mm. Degeneration in the horizontal fibre bands appears throughout the sections, but because the damage appears at different depths on adjoining sections the maximal degeneration in these bands is seen on different sections when the damage is at that level. The most important feature of the fibre degeneration is the obvious arrangement of many of the fragments in distinct rows perpendicular to the surface and corresponding to the bundles seen in normal material. These are present superficial and deep to the track, and more anteriorly are vertically disposed but at the bank of the sulcus become progressively oblique with the increasing

---

FIG. 3. A, B, The microelectrode lesion passing perpendicularly through the cortex shown in fig. 1 photographed on adjoining sections under dark field illumination. Bar = 500 μm. C, Part of the section shown in B at a higher magnification to illustrate a long length of a horizontal fibre at the level of the Betz cells. Bar = 250 μm. D, The lesion and immediately surrounding dense degeneration and fibres radiating in a tangential section of area 4, under dark field illumination. Bar = 100 μm. All photomicrographs shown in the plates have been taken from area 4 within 2 mm of the lesion and the sections have been stained by the Wiitanen (1969) method.


A
B
C
D


V
VI
A
V
VI
B
II
III
C

curvature of the cortex. In the Wiitanen sections these bundles of fragments lie between the adjoining rows of pyramidal cells separated by intervals of about 50 μm. The number of such vertically arranged fragments passing down through layer V increases close to the bank of the central sulcus underneath the deepest part of the lesion. A similar oblique penetration passing more superficially through the cortex of the anterior bank of the central sulcus does not extend deeper than layer III and the degeneration in the deeper layers, both horizontal and vertical, is much less than when the electrode has involved these layers directly (fig. 7B).

That the restricted extent of the degeneration found after microelectrode lesions is not due simply to the narrow and limited damage caused by the microelectrode is indicated by the findings after larger lesions made by inserting a needle. The damage is in the form of a wedge 1 to 2 mm in size and reaches to layer VI. The pattern and extent of the terminal and fibre degeneration are essentially the same as after a microelectrode track but the density is slightly greater close to the immediate damage. In some brains the microelectrode was driven into the cortex without current being passed, and the lesions and degeneration are indistinguishable from those made with the passage of current.

Similar lesions were studied in coronal sections, but because the sections were cut at varying degrees of obliquity to the electrode track the damage at different depths appeared on separate sections. In all respects but one the degeneration is the same as in the sagittal sections, and the difference is related to the horizontal fibres close to the Betz cells. For a width of 500 μm on either side of the dense degeneration these are similar in number and appearance to those found in the sagittal sections, but at this point there is a sudden diminution with only an occasional fragment present beyond. The long fragments which can be traced over a distance of a few millimetres at this depth in the cortex in sagittal sections are not seen. The degeneration does not extend beyond that found in the more superficial and deep layers, and it is the same on either side of the lesion. This difference in the extent and symmetry of the horizontal fibre degeneration in relation to the Betz cells in the sagittal and coronal planes has been confirmed in a planar reconstruction from measurements of its maximal extent in all of the sections in which it could be identified (fig. 8). The degeneration is maximal on sections through the lesion, its total extent in the sagittal plane is greater than in the coronal and it is asymmetrical anteroposteriorly but not mediolaterally. The anteroposterior extent of the degeneration can only be determined with certainty in the sagittal sections and the mediolateral extent in the coronal sections. A composite of the reconstructions

---

FIG. 4. A, The predominantly radial arrangement of the fibres in layers V and VI of the normal cortex of area 4. A small number of fibres can be seen passing horizontally through layer V. Bar = 100 μm. B, Bundles of degenerating fibres passing perpendicularly through layers V and VI following a microelectrode lesion. Note the similarity in the arrangement of these degenerating fibres to those in the normal cortex, and in both normal and experimental material the spacing of the fibre bundles at approximately 50 μm between vertical rows of nerve cells. Bar = 100 μm. C, Degeneration of the fibres in the horizontal plexus at the boundary of layers II and III. For Roman numerals *see* fig. 1. Bar = 50 μm.

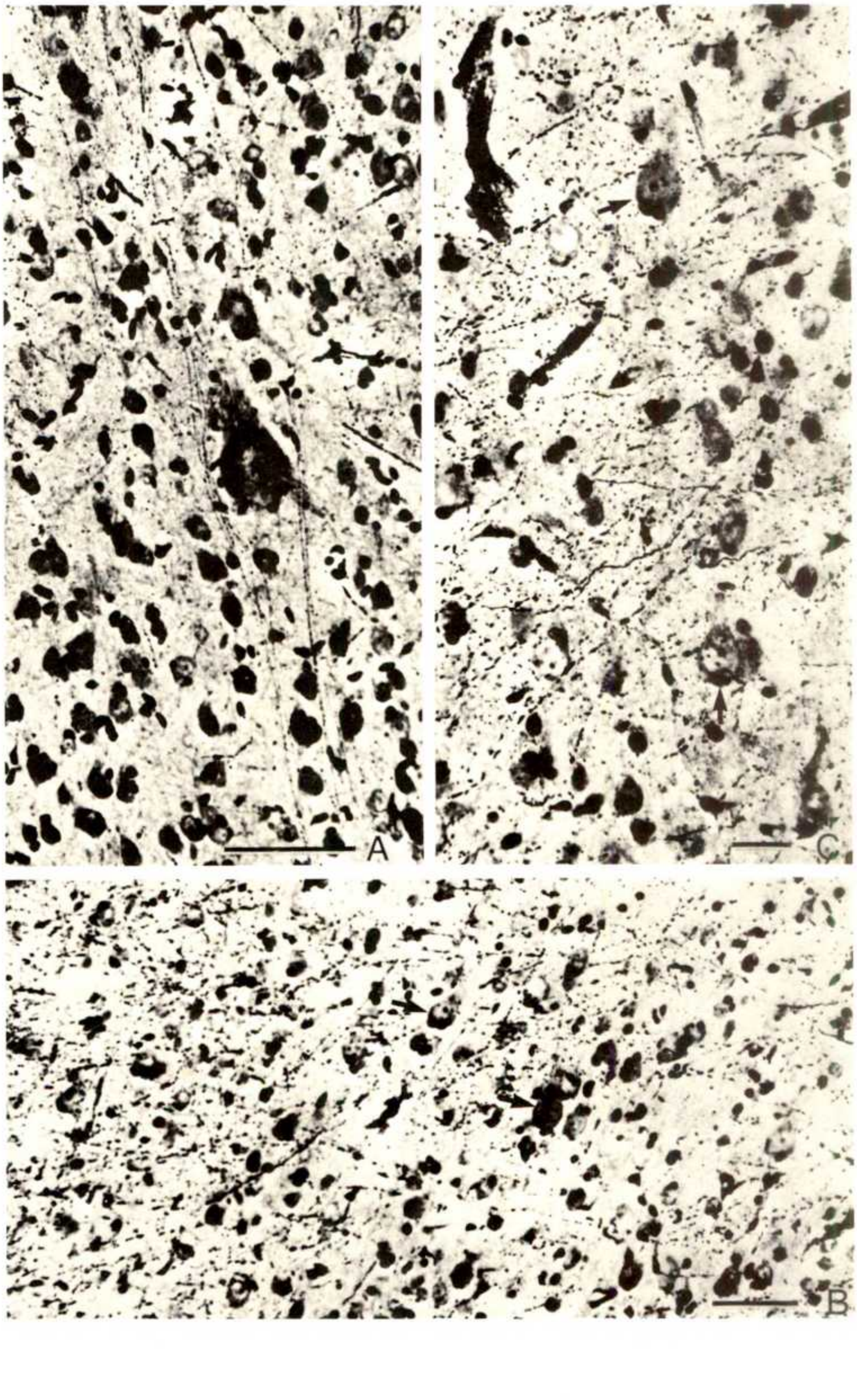
in these two planes would probably indicate that the tangential spread of the degeneration is in the shape of an ellipse, with its long axis directed anteroposteriorly. This interpretation is confirmed in sections cut tangential to the surface of the cortex (fig. 9). The electrode track appears as a clear hole 100 μm across and is immediately surrounded by a cuff of glial cells outside which there is a circular zone of dense fine degeneration 200 to 300 μm wide (fig. 3D, fig. 6C). The fact that the degeneration is outside this glial cuff indicates that it is not due to direct damage arising from the passage of the electrode. Beyond the zone of dense degeneration in the superficial layers there is a moderate degree of terminal degeneration for 1 to 2 mm but few fibre fragments. At the level of the Betz cells coarse fibre fragments appear (fig. 10) and these are aligned predominantly in the anteroposterior dimension and extend for 1 to 2 mm further in this dimension than mediolaterally. In the deeper parts of layers V and VI there are less degenerating fibres which are not as coarse as those at the level of the Betz cells.

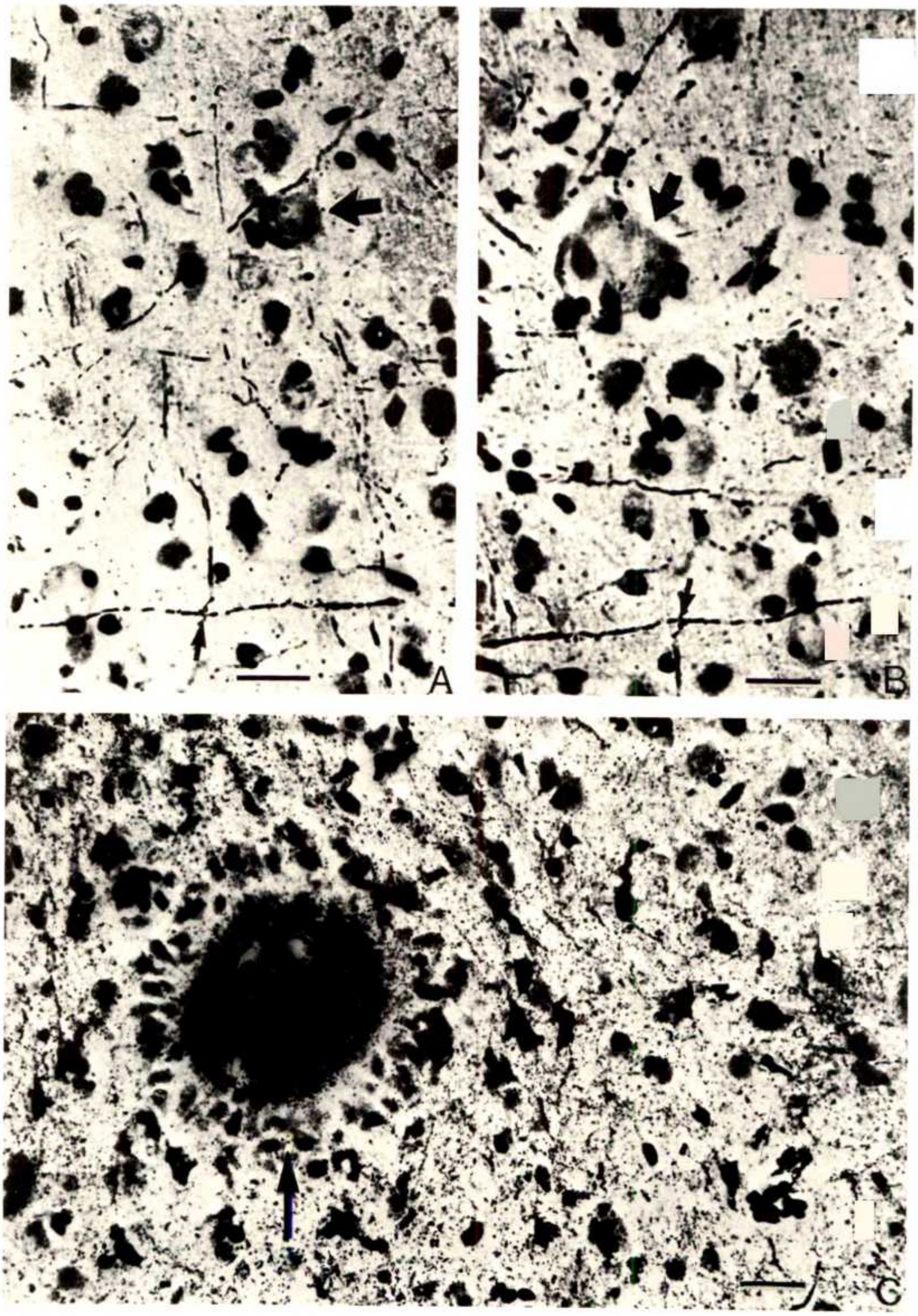
Another group of lesions, in which the damage does not extend through the full depth of the cortex, has given further information about the laminar origin of some of the intrinsic connections of the cortex. Although no specific lesion is restricted to layer I, in a few sections at sites quite distinct from lesions, small foci (around 500 μm) of fine granular degeneration are present in this layer. A few fibres pass sideways from the principal focus but no degeneration is seen deep to layer I. These foci are probably due to slight ischaemia caused by spasm of fine vessels.

A localized area of damage restricted to layers I and II is surrounded by fine degeneration for 1 to 2 mm and on its deep aspect a few fragmented fibres pass down into the superficial part of layer III but no degeneration can be seen deeper than this level.

When the damage extends deeper to involve the superficial half of layer III the pattern of degeneration is completely different. In layers I and II there is fine fibre and terminal degeneration on either side, and in layer III the fragments are coarser and are interspersed amongst a moderate degree of granular degeneration. At the junction of layers II and III the horizontal plexus of fine interweaving degenerating fibres is clearly seen. Below the lesion in the deep half of layer III there are more fragments and some are orientated perpendicularly and can be traced down between the Betz cells into layers V and VI and into the white matter. At the level of the Betz cells there are a few horizontal fragments of coarser fibres and the arrangement of these two sets of fibres at right angles to each other is clear because of the relative absence of any background degeneration. In addition to the vertically orientated fibres in layers V and VI there are some obliquely and transversely

FIG. 5. A, Fine degenerating fibres passing vertically around the soma of a Betz cell in layer V after an electrolytic lesion in the cortex. B, Horizontal plexus of degenerating fibres at the level of the Betz cells (arrows). The density of degeneration is greater on the left half of the figure, closer to the electrolytic lesion. C, Degeneration of the horizontal fibres around Betz cells (arrows); the plexus is somewhat obliquely disposed as a result of distortion by the adjoining lesion. Bars = 50 μm.


A
C
B


A
B
C

directed fibres. In all layers the degeneration does not extend more than 1 mm or so from the edge of the lesion and it is appreciably less dense than after penetrations into the deeper layers. The vertically orientated fibres passing down to the white matter occupy a restricted zone about 500 μm wide beneath the lesion. Lesions which extend as narrow tracks through the depth of layer III but stop immediately above the Betz cells cause degeneration which is the same as when only the superficial part of layer III is involved, except that there is a definite increase in the number of coarse fibre fragments arranged horizontally at the level of the Betz cells. Some of these pass downwards and sideways from the tip of the track. Several lesions extend deeply into layer V below the Betz cells, and this additional damage is accompanied by an increase in the amount of degeneration in layers III and V so that the appearance is essentially that of a full depth lesion. The number of vertically orientated fibres deep to the lesion is considerably greater than after lesions restricted to layer III and these can be traced through layer VI to the white matter. These fibres are confined within a strip of the same width as the dense degeneration above them. In layer VI there are some fragments and terminal degeneration irregularly arranged.

It has not been possible to make focal lesions virtually restricted to a particular lamina because passage of the electrode by itself resulted in appreciable degeneration. Some of the electrode tracks happened to be cut obliquely with successive portions on adjoining sections, and to all intents and purposes these could be considered as individual laminar lesions. Certain features are common to all of them: the width and appearance of the dense fine degeneration in the immediate vicinity of the track is the same all round; frequently there is little, if any, degeneration in the layers superficial and deep to the damage, and the fibre and terminal degeneration which is present in the immediate vicinity has the characteristics found at that level in sections in which most of the length of the track is present, a good example being the degeneration of an appreciable number of horizontal fibres at the level of the Betz cells found only when the damage is at that site; radially orientated degenerating fibres are invariably restricted to the width of the zone of dense degeneration and are coarser and more numerous on the deep aspect of the lesion.

The electrode was sometimes introduced close to the precentral dimples and arcuate sulcus at the anterior margin of area 4 or immediately in front of the central sulcus, with the intention of penetrating the cortex buried in the walls of these sulci. In one of these the electrode entered the cortex immediately posterior to the medial end of the anterior subcentral sulcus in the face region of area 4. In the sagittal sections the track passes vertically through the entire depth of the cortex of area 4 on the exposed surface and is slightly oblique to the radial organization of cells

---

FIG. 6. A, B, Degeneration of fibres in the horizontal plexus at the level of the Betz cells. Small arrows point to fibres passing horizontally in each photomicrograph and large arrows to Betz cells with degenerating fibres in close proximity to them. C, Microelectrode lesion in a tangential section of the cortex with a cuff of glial cells (arrow) immediately surrounding the damage, and outside this the zone of dense degeneration. Bars = 25 μm.

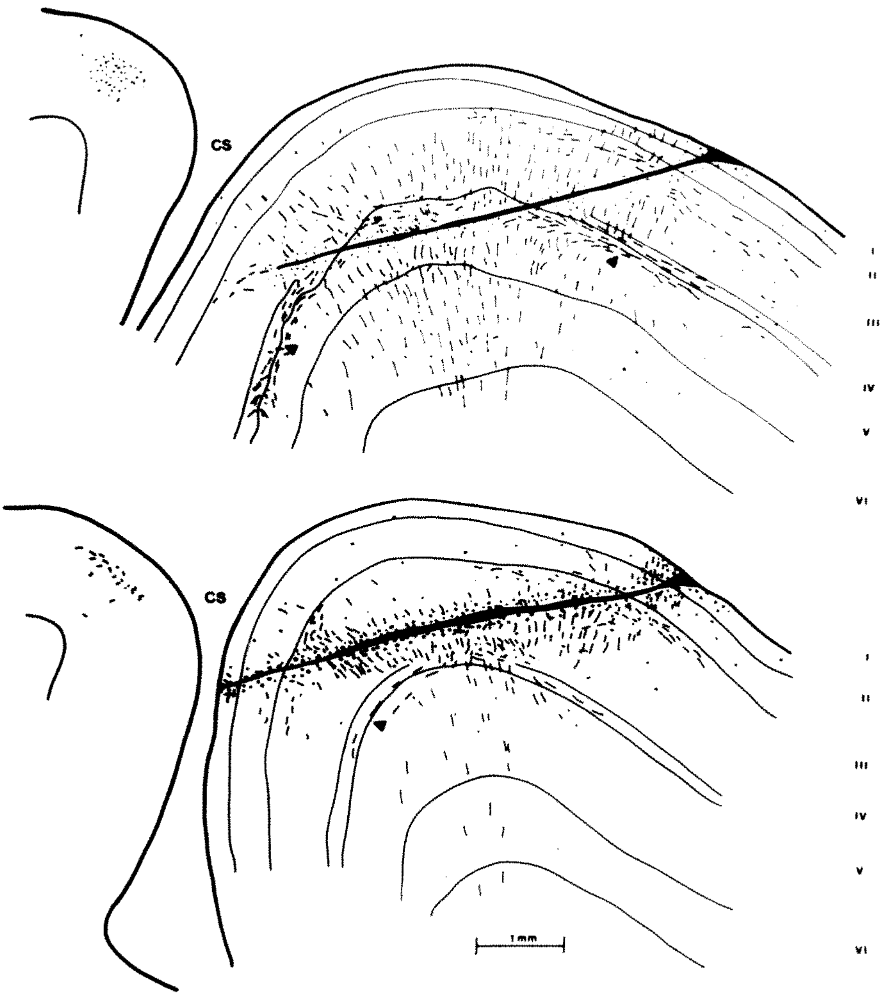


FIG. 7. The fibre and terminal degeneration in sagittal sections resulting from oblique penetrations. In the top figure the track passes deeply into layer V and in the lower it remains in the superficial three layers. For abbreviations *see* fig. 1.

and fibres (fig. 11). It reaches layer VI at the point when the cortex is turning sharply to form the posterior wall of the sulcus and from this point it remains at the same depth in the cortex, running tangentially through layer VI. At the bottom of the sulcus the track continues on for about a millimetre into the underlying white matter. The entire extent of the lesion is within area 4 as Betz cells can be traced uninterruptedly to just in front of the fundus of the sulcus. In the cortex of the exposed surface, the features and extent of the degeneration are the same as with a full depth lesion. The horizontal degenerating fibres at the level of the Betz cells

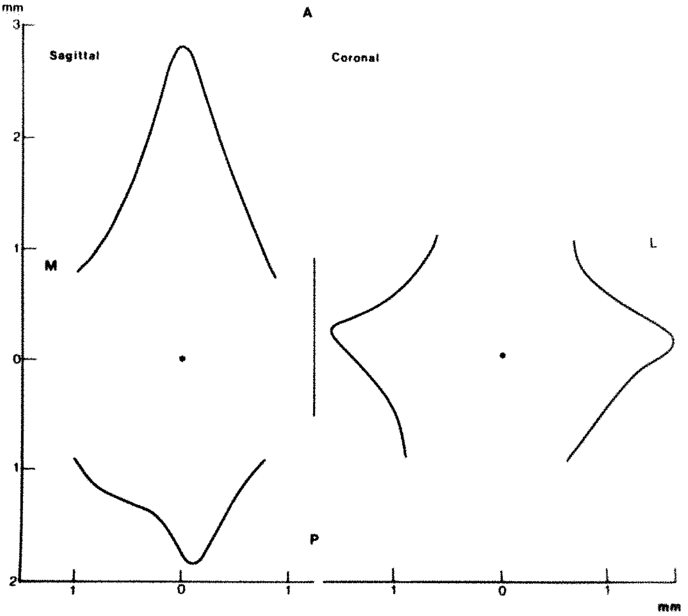


FIG. 8. Planar reconstructions of the maximum spread of horizontal fibre degeneration at the level of the Betz cells after a microelectrode lesion (large dot) as seen in sagittal sections (*left*) and coronal sections (*right*). For abbreviations *see* fig. 1.

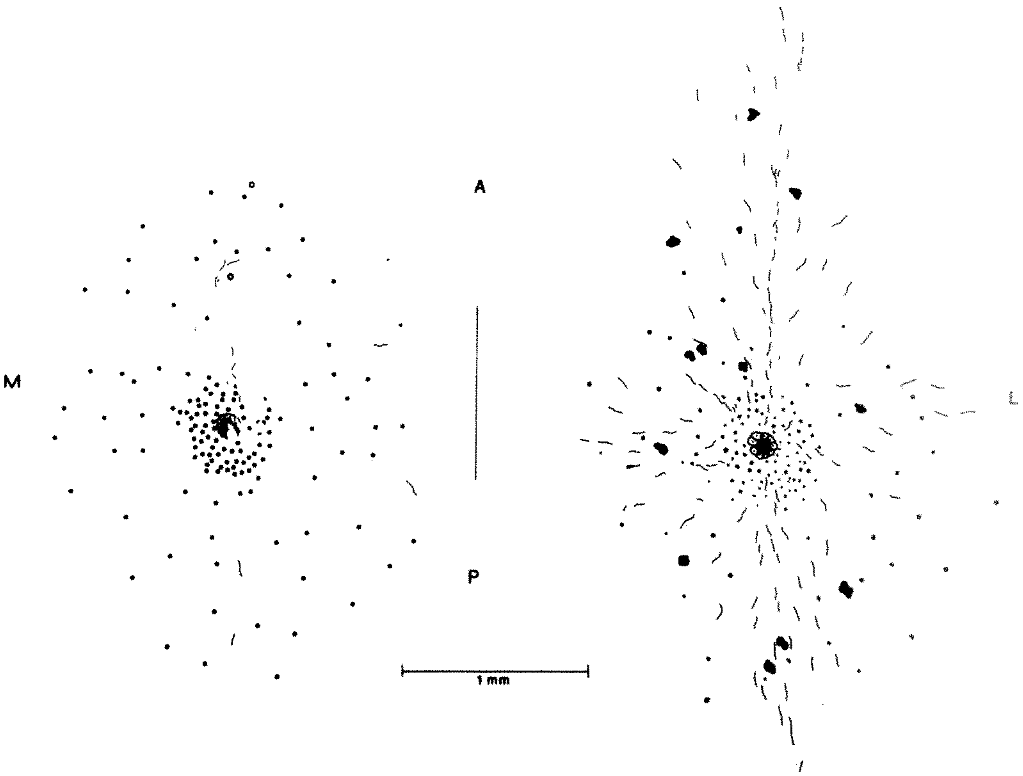
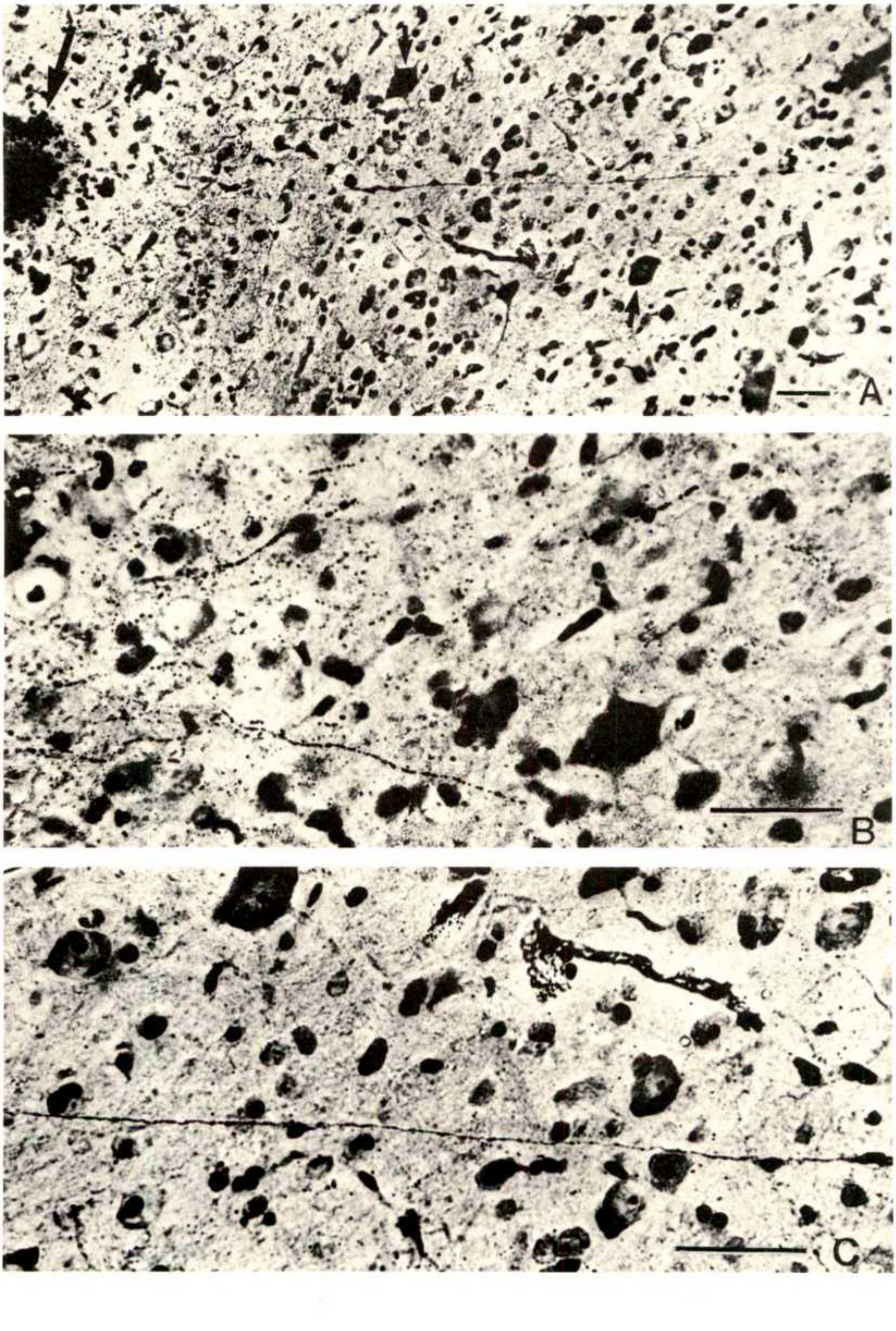


FIG. 9. The distribution of the fibre and terminal degeneration in tangential sections of the cortex; on the left is shown the degeneration at the level of layer II and on the right at the level of the Betz cells, the outlines of which were traced and filled in solid black. For abbreviations *see* fig. 1.


A
B
C

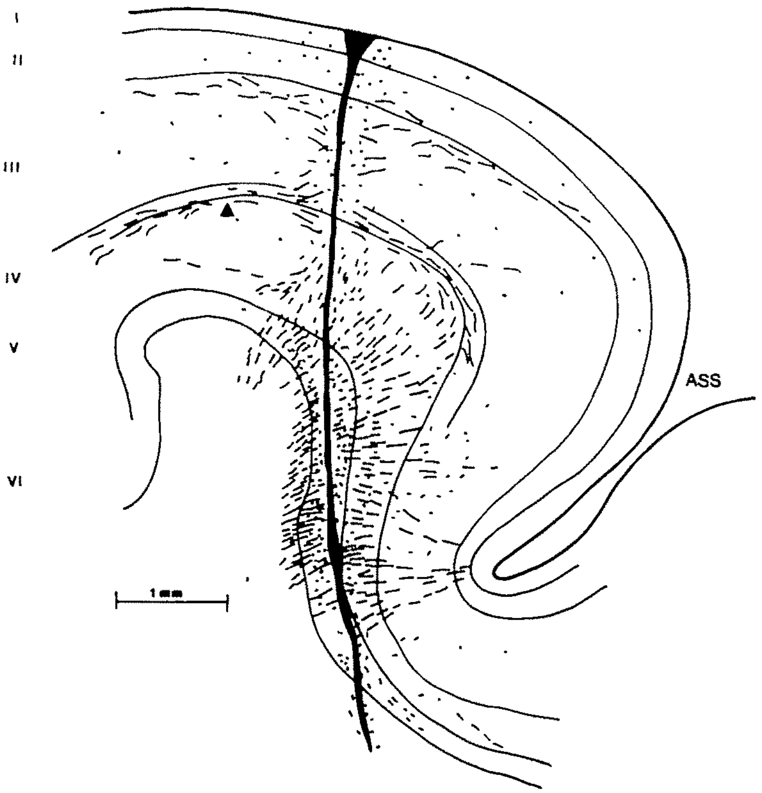


FIG. 11. An electrode track passing perpendicularly through the cortex on the lateral surface and continuing into the posterior wall of the precentral dimple where it passes tangentially through layer VI. For abbreviations *see* fig. 1.

reach anteriorly to the point in the bank of the sulcus which is perpendicularly in line with where the track reaches layer VI. In the wall of the dimple the pattern of degeneration is distinctly different, with the degenerating fibres being radially orientated in contrast to the predominantly horizontal disposition on either side of the perpendicular part of the track. Superficial to the track numerous fragments are in rows perpendicular to the surface, and these pass up to the level of the Betz cells where they suddenly diminish in number. An occasional fragmented fibre continues perpendicularly into layer III and some become obliquely disposed. Fine granular degeneration is present in most layers and is heaviest in the deep half of layer III, in layer IV and the superficial part of layer V. In layer VI deep to the lesion there is also heavy fibre and terminal degeneration, most of which is also arranged in rows at right angles to the surface. Conspicuous by their absence

---

FIG. 10. A, Microelectrode lesion (large arrow) in a tangential section at the level of the Betz cells (small arrows). B, C, Parts of A at higher magnifications. B is close to the lesion with dense degeneration in the left half of the figure and degenerating fibres radiating beyond this, in C is shown a long length of a degenerating horizontal fibre. Bars = 50 μm

are the bands of horizontally arranged fragments at the junction of layers II and III and at the level of the Betz cells. The only horizontally arranged degeneration is in layer VI close to the bottom of the sulcus where rows of fragments sweep forward. In the immediate vicinity of the track a few degenerating neurons are intensely stained giving an appearance similar to Golgi-impregnated cells. Rows of fragments representing the degenerating apical dendrites of these cells are interspersed amongst the degenerating axons and can readily be distinguished by their coarser size. This experiment combines a perpendicular and tangential lesion in immediately adjoining parts of area 4 and shows the pattern of fibre distribution in two dimensions of the cortex, vertical and tangential, and it also provides evidence that the fibres in the horizontal plexuses are predominantly intrinsic to the cortex.

In several vertical penetrations through the anterior bank of the central sulcus to various depths in the anterior wall of the sulcus and into the posterior bank and wall of the arcuate sulcus, the features of the degeneration were similar. Because of the marked curvature of the cortex in both the anteroposterior and mediolateral dimension at the banks of these sulci the degree of obliquity of the radial degeneration changes rapidly with increasing depth of the track. In some experiments the part of a track extending from the surface to layer V was present on one section with no radial degeneration in the layers deep to it, but a few sections away when the damage was no longer present the radial degeneration in the deep layers appears and is parallel and between the cell columns which are arranged literally radial to the curving arc of the cortical surface.

In that part of the representation of the distal forelimb in the depth of the anterior wall of the central sulcus the cortex does not show such a pronounced radial arrangement of the cell columns as on the exposed surface, but the arrangement of the intrinsic fibre connections appears to be the same as in the other parts of area 4.

DISCUSSION

The intrinsic fibre connections of area 4 appear to be limited to within a few millimetres of their origin and in both their pattern and extent are similar throughout the motor cortex irrespective of the topographic representation. In most of their features the intrinsic connections of area 4 and of area 17 of the visual cortex (Fisken *et al.*, 1975) are similar, which would suggest that they are organized upon a common principle. The measurements of the extent of these connections in the present histological material are of the same order as those made upon the extent of the motor cortex related to individual spinal motoneurons or muscles in electrophysiological experiments.

The dense finely granular degeneration present in all layers for approximately 200 to 300 μm on all aspects of the lesion is an indication of the distance over which the cortical neurons are strongly interconnected. The fact that the width and appearance of this degeneration was constant in all layers and parts of the cortex with different types of lesions and whether or not a current was passed supports the interpretation of the granularity as being indicative of neuronal interconnections rather than simply a reflection of direct damage. This is further supported by the appearance in tangential sections of a distinct cuff of glial cells separating the electrode track and the dense degeneration. The dense degeneration stops suddenly and beyond it there is a moderate degree of fibre and terminal degeneration for 2 to 3 mm. Throughout most of the superficial layers there are few fibres and these are fine but in the deeper layers they are more numerous and coarser. At the junction of layers II and III and in layer IV there are accentuations of the horizontal fibres into distinct bands and the latter forms one of the most prominent features of the degeneration. The extent of this degeneration in the sagittal plane is the maximum seen for degeneration in any layer, and the close relationship to the Betz cells suggests a functional relationship. Throughout the rest of layer V there are a number of degenerating fibres arranged horizontally and sometimes these are accentuated near its deep margin, perhaps forming an inner band of Baillarger. The fibre degeneration after a narrow vertical lesion indicates the pattern and extent of the fibre connections *spreading out* from the damaged part of the cortex to influence other neurons within these limits, but these neurons are also *receiving* similar horizontal connections from other cells within a radius of a few millimetres in any direction.

These findings after perpendicular lesions through the whole depth of the cortex provide information mainly about the horizontal distribution of the intrinsic connections. Information on the vertical arrangement and laminar origin has been obtained from penetrations which either did not pass perpendicularly through the full depth of the cortex or which passed obliquely to the surface. If the damage is restricted to layers I and II the degeneration is also confined mainly to these layers with only a few fibres extending into the superficial part of layer III. With additional involvement of layer III degenerating vertical fibres pass down through the deeper layers and are restricted to the width of the lesion and the dense degeneration around it. At the level of the Betz cells there are a few coarse fibres passing horizontally, and in layers V and VI there are some transverse and obliquely degenerating fragments, indicating that layer III is sending fibres to layers V and VI as well as a small number into the white matter. The number of the vertically orientated fibres entering the white matter increases with involvement of layers V and VI, showing that most of the efferent fibres of the cortex probably arise from these layers, but they always remain restricted to essentially the width of the lesion and the zone of dense degeneration around it. The degeneration of the horizontal fibres at the level of the Betz cells is greatest when this layer is damaged, and there is more intrinsic and widespread degeneration in both layers III and V when the damage extends down to the deepest layers, in part through axon collaterals of efferent fibres from cells in layer V as well as short connections from cells in this layer. When the electrode passed tangentially for some distance in layer VI there were no degenerating horizontal fibres in layer IV superficial to the damage, indicating that most if not all of these fibres arise within the cortex.

The restricted extent of the vertically disposed fibres after perpendicular penetrations indicates that their course within the cortex is perpendicular with respect to their cells of origin. Penetrations oblique to the cortex confirm this finding and show that it is also true for the incoming afferent fibres to the cortex; the degenerating axons both superficial and deep to the lesion are regularly arranged between the columns or rows of cells at intervals of approximately 50 μm. With these oblique penetrations the extent of the dense fine degeneration both superficial and deep to the damage was approximately 200 to 300 μm—the same as on each side of the vertical lesions. The short intrinsic cortical axons appear to be distributed predominantly horizontally and within their laminæ of origin, although some pass obliquely between laminæ, particularly interconnecting layers III, V and VI. Many of these obliquely disposed fragments represent degenerating collateral branches of efferent axons and terminal branches of afferent fibres, and the extent of the degeneration conforms with measurements of these processes in Golgi material—1 mm for the intracortical branching of thalamocortical fibres (Asanuma, Fernandez, Scheibel and Scheibel, 1974) and 3 mm for the spread of axon collaterals (Scheibel and Scheibel, 1970).

These basic features of the organization of area 4 have also been found in areas as different, structurally and functionally, as area 17 (Fisken *et al.*, 1975), the first somatic sensory cortex (Vogt and Pandya, 1978; Shanks, Pearson and Powell, 1978) and area 5 of the parietal lobe (unpublished observations) of the same species, and in the visual cortex of the cat (Creutzfeldt *et al.*, 1977). There are, however, certain differences and, as would be expected from the cytoarchitecture, these are mainly related to layer IV and the outer band of Baillarger which are so well developed in area 17 and are at their minimum in area 4. The number of horizontal fibres at this level in area 4 is much less than in area 17 and the asymmetry and total extent of this fibre degeneration was not as obvious as in area 17. In the motor cortex, outside the 200 to 300 μm zone of fine degeneration, the density of the fibre and terminal degeneration was also less than in area 17. In area 17 the horizontal extent of the terminal degeneration in layer IV was limited to within 200 to 300 μm but in the motor cortex it was difficult to be certain that this was so, partly because layer IV is so narrow and also because the line of Betz cells and associated fibre fragments was irregular. Degeneration restricted to a separate inner band of Baillarger deeper in layer V was also not as obvious in area 4 as in visual cortex as fragmented horizontal fibres were present through the depth of this layer. The plexus of fine fibres at the junction of layers II and III seen clearly in the motor cortex had no counterpart in area 17.

It has been suggested that in the visual cortex 'the stria is a concentrated band of fibres which is closely related to the cells receiving the afferent fibres from the thalamus and that it may be considered as one of the first intracortical connections underlying the processing of information' (Fisken *et al.*, 1975). A clue to the possible significance of the comparable horizontal fibres in the motor cortex is provided by findings from Golgi studies (Cajal, 1911; Marin-Padilla, 1969, 1970) in which similar fibres, a millimetre or more in length and with a predominantly sagittal orientation, have been described. These axons arise from stellate cells in layers II, III and IV, are concentrated in horizontal plexuses at the boundary of layers II and III and in layer IV, and terminate in dense pericellular baskets around the somata of the large pyramidal cells above and below them in layers III and V. In the visual cortex the horizontal fibres in the stria of Gennari are between the laminæ in which the geniculocortical fibres terminate (Hubel and Wiesel, 1969, 1972; Garey and Powell, 1971) and it is probable that the majority of them arise and end within these laminæ (Fisken *et al.*, 1975). In the motor cortex the afferent fibres from the thalamus terminate in the deep half of layer III, in layer IV and the upper part of layer V (Sloper, 1973*b*; Strick and Sterling, 1974) and so there is again the same relationship of the horizontal fibres in layer IV with the thalamocortical fibres.

In both areas electron microscopic studies have shown that the thalamocortical fibres end upon the dendrites and somata of stellate neurons and have provided some evidence for a termination upon the apical dendrites of pyramidal cells (Sloper, 1973*b*; Strick and Sterling, 1974; Winfield and Powell, 1976). There is electrophysiological evidence for antidromically identified pyramidal tract neurons (PTN) and interneurons at the same cortical level in area 4 being monosynaptically excited upon stimulation of the ventrolateral nucleus of the thalamus (Amassian and Weiner, 1966; Yoshida, Yajima and Uno, 1966; Stone, 1973) and also that some of these interneurons in turn are inhibitory to the PTNs (Stefanis, 1969; Stone, 1973); from electron microscopic studies it would seem likely that some of the symmetrical axon terminals on the somata and dendrites of pyramidal neurons in layer V are from stellate cells (Sloper, 1973*b*). It has been suggested that the horizontal fibres in layer IV of the visual cortex are interconnecting independent groups of neurons in receipt of geniculocortical afferents (Fisken *et al.*, 1975) and the same appears to be true in area 4. As two distinct types of neurons are involved in area 4, the stellate or interneuron and the pyramidal, it might be reasonable to suggest now for *both areas*, in view of all the other similarities in their intrinsic organization, that the horizontal fibres in layer IV form a connection, inhibitory in function, between an interneuron and an output cell which are both receiving a direct input from the thalamus and which may be separated from each other by up to 2–3 mm. Whether the same correlations can be made for the horizontal fibres at the level of layers II and III and in the deeper part of layer V remains to be determined. This interpretation of the evidence suggests a basic similarity in the organization and function of the horizontal fibres in the visual and motor areas, but the obvious differences between the areas must also be taken into account. In area 17 layer IV and the horizontal fibres forming the stria of Gennari are maximally developed, probably in relation to the processing of sensory information, whereas in area 4 it is the pyramidal cell layers (III and V) which have increased relatively, with layer IV barely distinguishable.

Electrical stimulation of the cortex has been used extensively to analyse the influence of the motor cortex upon movement and essentially two methods have been used, surface stimulation with focal electrode and weak intracortical microstimulation. In both of these methods the pyramidal tract cells may be influenced by direct electrical excitation, with which we will not be concerned in this discussion, and with surface stimulation the effects of such direct activation of PTNs can be differentiated from indirect synaptic activation. With the weak current used in intracortical microstimulation it was initially considered that most of the effects were due to direct activation of the cells (Asanuma, Stoney and Abzug, 1968; Stoney, Thompson and Asanuma, 1968) but, as Jankowska, Padel and Tanaka (1975*a*) found that the effects of such stimulation are mainly indirect they concluded that '. . . the final functional interpretation of the effects of the intracortical stimulation will depend greatly on the network of the intracortical connections'. It is probably reasonable to assume that the extent of the degeneration of intracortical fibres found in the present experiments is of the same magnitude as the distance over which intracortical stimulation would have its effects and even that the present measurements may be an underestimate because microstimulation might activate cells and fibres slightly beyond the zone directly damaged by our lesions. In attempting to relate the histological findings with those obtained by electrical stimulation of the motor cortex one must be cautious because apart from the lack of information about the synaptic organizations within the cortex, there are many obvious gaps in our knowledge: the cells of origin of the different fibres; the inability to distinguish between short axons of interneurons, collateral branches of efferent and terminal branches of afferent fibres, and the types of synapses made and the parts of the neuron upon which these end.

With these qualifications the anatomical observations are in striking agreement with the electrophysiological findings of Asanuma and Rosén (1973) upon the spread of mono- and polysynaptic connections in the motor cortex of the cat. These authors recorded postsynaptic potentials evoked in cortical cells in response to microstimulation with 4 μA, and found that the majority of the cells monosynaptically influenced were within 400 μm *horizontally* from the site of stimulation (their fig. 7) and that polysynaptic effects were much wider for up to 1200 μm. The cells being influenced monosynaptically are probably those within the zone of dense degeneration and normally in receipt of numerous interconnections. Monosynaptic effects were not found beyond this point, possibly because the connections are considerably more sparse but polysynaptic effects may be occurring over this distance through convergence. The fact that Asanuma and Rosén (1973) found postsynaptic potentials in only one-third of the cells from which intracellular recordings were obtained may be due to the cells receiving fibres not only from neurons close to the stimulating electrode but also from cells in all other directions within a radius of a few mm. Stimulation of the superficial cortex down to 0·7 mm resulted in monosynaptic responses most of which were within the same depth or only slightly deeper, which would be in accord with the histological findings that damage of layers I and II did not result in degeneration extending more deeply than layer III; polysynaptic responses after stimulation in these layers were found in the deeper layers in agreement with the finding of degeneration in layers V and VI after lesions extending into layer III, the cells of origin of these fibres having received a synapse from cells in layers I and II. The present experiments have emphasized the horizontally disposed fibre fragmentation at the level of the Betz cells and stimulation in these middle layers of the cortex resulted in both mono- and polysynaptic responses predominantly at this and slightly deeper levels. Stimulation of the deeper layers of the cortex resulted in the majority of the responses being in the superficial layers and because this was not found with stimulation of the intermediate layers Asanuma and Rosén (1973) considered that the 4 μA stimulation excited cell bodies rather than myelinated fibres. Further support for this interpretation would be that all incoming fibres terminate in asymmetric, presumed excitatory, terminals whereas the majority of these monosynaptic responses in the superficial layers was inhibitory. These findings of postsynaptic potentials mainly in the superficial layers upon stimulation of the deeper layers would be in accord with histological observations of increased degeneration in layer III after involvement of the deep layers, and as Asanuma and Rosén (1973) mention, some at least of the excitatory effects could be through axon collaterals of pyramidal cells. The fact that these electrophysiological experiments were done in the cat and the present studies in the monkey does not invalidate these correlations as essentially the same pattern of degeneration after intracortical lesions is found in the cat (Creutzfeldt *et al.*, 1977; our own unpublished observations).

It has been possible to make certain functional correlations with the spread of the intrinsic connections in the horizontal dimension and it would be expected that the equally clear pattern in the vertical dimension would reflect some functional properties of the cortex. The clear columnar arrangement of the cells together with the strictly perpendicular disposition of the fibres at a regular spacing of approximately 50 μm is probably the basis for the columnar organization of neurons with the same peripheral receptive fields in the cat (Welt, Aschoff, Kameda and Brooks, 1967) and monkey (Rosén and Asanuma, 1972). Welt *et al.* (1967) considered that cells with receptive fields in the same part of the body surface were arranged in radially orientated arrays and that 'the mean cross column distance within which adequate stimuli were similar was only 50 μm for each type of stimulus', and Rosén and Asanuma (1972) that 'the cells, driven by peripheral stimulation, are sparsely scattered in radial columns'.

The degenerating vertically arranged fibres superficial and deep to a perpendicular or localized lesion are always restricted to a narrow zone (approximately 0·5 to 1·0 mm diameter) equivalent in width to that of the dense granular degeneration. The degenerating fibres which are deep to the damage are mainly efferent fibres, and as they arise only from within the zone of dense degeneration and pass in a strictly radial direction it would seem that this extent of cortex is the anatomical equivalent of the efferent zones for a given movement which have been shown by intracortical microstimulation to be of the same size, 1 mm or a little less, columnar in shape and distributed along the direction of the radial fibres (Asanuma and Rosén, 1972). The number of degenerating axons entering the white matter increased with damage of layers V and VI which agrees with the conclusion from microstimulation experiments that the probability of producing a motor effect was highest in layer V (Asanuma and Rosén, 1972; Andersen *et al.*, 1975). As many of the degenerating fibres superficial to the damage are afferent to the cortex and as the zone of dense degeneration represents an extent of cortex which is densely interconnected, it is also likely that with respect to its extrinsic afferent and efferent connections a vertical cylinder through the cortex of this dimension corresponds to the input-output zone of 1 mm or less described by Rosén and Asanuma (1972). These authors found that the cells within a low threshold efferent zone were activated by stimulation of the skin, muscles and joints within a region closely related to the movement elicited by intracortical stimulation of that zone, and from the joints and muscles taking part in the movement; just as the degenerating efferent fibres from the cortex have been found to arise only from within the zone of dense degeneration, the afferent fibres from the thalamus have been shown to branch over the same horizontal extent of 1·0 millimetre (Strick, 1973; Asanuma *et al.*, 1974). However, these zones cannot be discrete and independent, (Lemon, Hanby and Porter, 1976) because although a cell in the middle of such a cylinder will be strongly related to cells within 0·5 mm in any horizontal direction, cells nearer the edge of the cylinder will be similarly related to neurons progressively further away. One has therefore a series of overlapping input-output or lowest threshold zones (Andersen, Hagan, Phillips and Powell, 1975). It is probable that this zone of dense degeneration and the related group of efferent fibres also corresponds to the smaller colonies or 'best points' of Landgren, Phillips and Porter (1962) and the maximum projection areas of Jankowska *et al.*, (1975*b*) defined with surface anodal stimulation and with the lowest threshold cores to intracortical stimulation of Andersen *et al.*, (1975).

The less severe degeneration which extends over a distance of a few millimetres represents intrinsic fibre and axon collateral connections which must provide the basis for further overlap and functional interrelationships, although progressively less marked, between adjoining cells in the cortex. The extent of this degeneration and its asymmetrical distribution corresponds with the measurements of the colonies of cortical neurons projecting upon individual spinal motor neurons determined by anodal stimulation of the surface of the cortex (Landgren, Phillips and Porter, 1962; Asanuma and Rosén, 1972; Jankowska *et al.*, 1975*b*), and the aggregations of colonies found on intracortical stimulation by Andersen *et al.* (1975). In other words, it would seem that the intrinsic fibre connections spread over the distance which includes the cells projecting directly to one motoneuron. The presence of intrinsic connections extending over this distance might also explain the overlap of neurons related to different muscles which has been found by all these workers. With regard to the influence of area 4 upon the spinal cord, the experiments using electrical stimulation suggest that there are two functional zones of cortex, one of 0·5 to 1·0 mm and another of a few millimetres in extent, and in the case of each of these there is overlap between different muscles (Jankowska *et al.*, 1975*b*). Anatomically, the connections are also organized in two distinct ways which differ both in intensity and extent: within an extent of 0·5 to 1·0 mm there are dense horizontal intrinsic connections together with the origin and termination of the radial efferent and afferent fibres, and over a radius of a few millimetres there are fewer intrinsic connections together with the axon collaterals of efferent fibres. To what extent these two patterns of anatomical connections form the basis of the two functional zones is uncertain, but they do indicate that although the neurons within a vertical cylinder of 0·5 to 1·0 mm radius may form a functional column, no groups of cells can be functionally independent of other cells within the adjoining few mm of cortex. Variation in the functional activity of these intrinsic connections due to previous stimulation of the same or adjoining region of cortex is probably the basis of the variation of the details of the response to surface stimulation, as suggested by Leyton and Sherrington many years ago (1917).

Landgren *et al.* (1962) found that when the threshold surface-anodal current required to excite directly a single pyramidal cell was plotted against distance from the lowest threshold point on the cortex for the same cell, the spread of the curves was wider in the mediolateral direction than anteroposteriorly and there was slight asymmetry in each direction. As these authors considered that no physiological or synaptic spread was involved in these measurements no clear correlation can be made with the present findings, but it is significant that experiments with such different techniques have both shown a difference between the organization along the anteroposterior and mediolateral dimensions of the cortex and it would be important to determine if there is a relationship between the anatomical and functional observations.

As the strictly intrinsic axonal connections appear to be disposed predominantly in the horizontal dimension and the vertical axons are mainly those of the afferent and efferent pathways, it is perhaps worth emphasizing that the neuronal processes which do form links between the different layers of the cortex are the apical and basal dendrites of the pyramidal cells; a pyramid in layer III could be influenced by axon terminals in the superficial four layers of the cortex, and one in layer V by terminals in all layers.

There are marked similarities in the pattern and extent of the fibre degeneration after intracortical lesions in the visual and motor areas, and functional correlations have been suggested for each of these areas. The importance of the column in the sensory areas has usually been discussed in relation to the processing of afferent information from the sensory receptors, while the role of those in area 4 has been considered mainly in relation to its efferent influence on muscles. In each of these areas, however, the column contains both efferent (pyramidal) and interneuronal cells in the same proportions, approximately two-thirds pyramidal and one-third non-pyramidal (Sloper, 1973*a*). Thus the column in the sensory and motor area is both an input and an output zone, with most of the pyramids in the superficial layers sending fibres to the other cortical areas of the same or opposite hemisphere and those in the deep layers projecting to subcortical sites. In both areas the single cell-wide columns have been correlated with the peripheral receptive field, 25–50 μm wide (Hubel and Wiesel, 1974*a*) in the visual and 50 μm in the motor cortex (Welt, Aschoff, Kameda and Brooks, 1967). In the visual cortex the 0·5 to 1·0 mm wide zone of dense degeneration has been suggested (Fisken *et al.*, 1975) as being the basis of the hyper column related to ocular dominance or orientation (Hubel and Wiesel, 1974*b*) and in the motor cortex as an 'input-output' zone. The moderate degeneration over 2 to 3 mm in area 17 may represent the connections within the area suggested by Hubel and Wiesel (1974*b*) to contain 'by a comfortable margin the machinery it needs to analyse the region of visual field that it subserves', and the question now arises whether the similar extent of cortex in the motor area has an equivalent function in relation to a particular part of the body.

SUMMARY

The intrinsic connections of area 4 of the monkey have been investigated with axonal degeneration methods after the placement of microelectrode lesions within the cortex. The fibre degeneration is restricted to within a few millimetres of the damage and is asymmetrically distributed in the form of an ellipse with its long axis anteroposteriorly. The same pattern is found in all topographic subdivisions of the motor cortex. There are two distinct zones of degeneration, dense fine terminal degeneration for 200 to 300 μm all around the lesion, and a moderate degree of fibre terminal degeneration for a further 2 to 3 mm. The intrinsic connections are disposed predominantly in a horizontal or oblique direction and within the laminæ of origin, but there are fibres passing between adjoining laminæ and between layers III and V and VI. Two horizontal plexuses of degenerating fibres are present, at the boundary of layers II and III and at the level of the Betz cells, and these fibres arise within the cortex. The afferent and efferent fibres of the cortex are arranged strictly perpendicular to the surface. The extent and pattern of the intrinsic connections of area 4 are very similar to those of area 17 of the visual cortex.

ACKNOWLEDGEMENTS

This work was carried out with the aid of grants from the Medical and Science Research Councils and the Wellcome Trust.

REFERENCES

AMASSIAN, V. E. and WEINER, H. (1966) Monosynaptic and polysynaptic activation of pyramidal tract neurons by thalamic stimulation. In: *The Thalamus*. Edited by D. P. Purpura and M. D. Yahr. New York: Columbia University Press, pp. 255-286.

ANDERSEN, P., HAGAN, P. J., PHILLIPS, C. G. and POWELL, T. P. S. (1975) Mapping by microstimulation of overlapping projections from area 4 to motor units of the baboon's hand. *Proceeding of the Royal Society, London*, Series B, **188**, 31-60.

ASANUMA, H., FERNANDEZ, J., SCHEIBEL, M. E. and SCHEIBEL, A. B. (1974) Characteristics of projections from the nucleus ventralis lateralis to the motor cortex in the cat: an anatomical and physiological study. *Experimental Brain Research*, **20**, 315-330.

ASANUMA, H. and ROSÉN, I. (1972) Topographical organization of cortical efferent zones projecting to distal forelimb muscles in the monkey. *Experimental Brain Research*, **14**, 243-256.

—— —— (1973) Spread of mono- and polysynaptic connections within cat's motor cortex. *Experimental Brain Research*, **16**, 507-520.

—— STONEY, S. D. Jr. and ABZUG, C. (1968) Relationship between afferent input and motor outflow in cat motorsensory cortex. *Journal of Neurophysiology*, **31**, 670-681.

CAJAL, S. R. y. (1911) *Histologie du Système nerveux de l'Homme et des Vertébrés*, Vol. II. Paris: Maloine.

CREUTZFELDT, O. D., GAREY, L. J., KURODA, R. and WOLFF, J.-R. (1977) The distribution of degenerating axons after small lesions in the intact and isolated visual cortex of the cat. *Experimental Brain Research*, **27**, 419-440.

FERRIER, D. (1873) Experimental researches in cerebral physiology and pathology. *West Riding Lunatic Asylum Medical Report*, **3**, 1-50.

FINK, R. P. and HEIMER, L. (1967) Two methods for selective silver impregnation for degenerating axons and their synaptic endings in the central nervous system. *Brain Research, Amsterdam*, **4**, 369-374.

FISKEN, R. A., GAREY, L. J. and POWELL, T. P. S. (1975) The intrinsic, association and commissural connections of area 17 of the visual cortex. *Philosophical Transactions of the Royal Society*, Series B, **272**, 487-536.

FRITSCH, G. and HITZIG, E. (1870) Über die elektrische Erregbarkeit die Grosshirns *Archiv für Wissenschaftliche Medizin* 300-332. (Extract translated from the German by D. Harris. In: *Brain and Behaviour* (1969), vol. 2, pp. 353-364. London: Penguin).

GAREY, L J. and POWELL, T. P. S. (1971) An experimental study of the termination of the lateral geniculocortical pathway in the cat and monkey. *Proceedings of the Royal Society of London*, Series B, **179**, 41-63.

HERN, J. E. C., LANDGREN, S., PHILLIPS, C. G. and PORTER, R. (1962) Selective excitation of corticofugal neurones by surface-anodal stimulation of the baboon's motor cortex. *Journal of Physiology, London*, **161**, 73-90.

HUBEL, D. H. (1957) Tungsten microelectrode for recording from single units. *Science, New York*, **125**, 549-550.

—— and WIESEL, T. N. (1969) Anatomical demonstration of columns in the monkey striate cortex. *Nature, London*, **221**, 747-750.

HUBEL, D. H. and WIESEL, T. N. (1972) Laminar and columnar distribution of geniculo-cortical fibers in the macaque monkey. *Journal of Comparative Neurology*, **146**, 421–450.

—— —— (1974*a*) Sequence regularity and geometry of orientation columns in the monkey striate cortex. *Journal of Comparative Neurology*, **158**, 267–294.

—— —— (1974*b*) Uniformity of monkey striate cortex: A parallel relationship between field size, scatter, and magnification factor. *Journal of Comparative Neurology*, **158**, 295–306.

JANKOWSKA, E., PADEL, Y. and TANAKA, R. (1975*a*) The mode of activation of pyramidal tract cells by intracortical stimuli. *Journal of Physiology, London*, **249**, 617–636.

—— —— —— (1975*b*) Projections of pyramidal tract cells to α-motoneurones innervating hind-limb muscles in the monkey. *Journal of Physiology, London*, **249**, 637–667.

LANDGREN, S., PHILLIPS, C. G. and PORTER, R. (1962) Cortical fields of origin of the monosynaptic pyramidal pathways to some alpha motoneurones of the baboon's hand and forearm. *Journal of Physiology, London*, **161**, 112–125.

LEMON, R. N., HANBY, J. A. and PORTER, R. (1976) Relationship between the activity of precentral neurones during active and passive movements in conscious monkeys. *Proceeding of the Royal Society of London*, Series B, **194**, 341–373.

LEYTON, A. S. G. and SHERRINGTON, C. S. (1917) Observations on the excitable cortex of the chimpanzee, orang-utan and gorilla. *Quarterly Journal of Experimental Physiology*, **11**, 135–222.

LIDDELL, E. G. T. and PHILLIPS, C. G. (1950) Thresholds of cortical representation. *Brain*, **73**, 125–140.

—— —— (1952) The cortical representation of motor units. *Brain*, **75**, 510–525.

MARIN-PADILLA, M. (1969) Origin of the pericellular baskets of the human motor cortex: a Golgi study. *Brain Research, Amsterdam*, **14**, 633–646.

—— (1970) Prenatal and early postnatal ontogenesis of the human motor cortex: a Golgi study. 2. The basket-pyramidal system. *Brain Research, Amsterdam*, **23**, 185–191.

NAUTA, H. J. W., BUTLER, A. B. and JANE, J. A. (1973) Some observations on axonal degeneration resulting from superficial lesions of the cerebral cortex. *Journal of Comparative Neurology*, **150**, 349–360.

ROSÉN, I. and ASANUMA, H. (1972) Peripheral afferent inputs to the forelimb area of the monkey motor cortex: input-output relations. *Experimental Brain Research*, **14**, 257–273.

SCHEIBEL, M. E. and SCHEIBEL, A. B. (1970) Elementary processes in selected thalamic and cortical subsystems—the structural substrates. In: *The Neurosciences Second Study Program*. Edited by F. O. Schmitt. New York: The Rockefeller University Press, pp. 443–457.

SHANKS, M. F., PEARSON, R. C. A. and POWELL, T. P. S. (1978) The intrinsic connections of the primary somatic sensory cortex of the monkey. *Proceedings of the Royal Society of London*, Series B. **200**, 95–101.

SLOPER, J. J. (1973*a*) An electron microscopic study of the neurons of the primate motor and somatic sensory cortices. *Journal of Neurocytology*, **2**, 351–359.

—— (1973*b*) An electron microscope study of the termination of afferent connections to the primate motor cortex. *Journal of Neurocytology*, **2**, 361–368.

SPATZ, W. B., TIGGES, J. and TIGGES, M. (1970) Subcortical projections, cortical associations, and some intrinsic interlaminar connections of the striate cortex in the squirrel monkey (*Saimiri*). *Journal of Comparative Neurology*, **140**, 155-174.

STEFANIS, C. (1969) Interneuronal mechanisms in the cortex. In: *The Interneurone*. Edited by M. A. B. Brazier. Los Angeles: University of California Press, pp. 497-526.

STONE, T. W. (1973) Cortical pyramidal tract interneurones and their sensitivity to L-glutamic acid. *Journal of Physiology, London*, **233**, 211-225.

STONEY, S. D. Jr., THOMPSON, W. D. and ASANUMA, H. (1968) Excitation of pyramidal tract cells by intracortical microstimulation: effective extent of stimulating current. *Journal of Neurophysiology*, **31**, 659-669.

STRICK, P. L. (1973) Light microscopic analysis of the cortical projection of the thalamic ventrolateral nucleus in the cat. *Brain Research, Amsterdam*, **55**, 1-24.

—— and STERLING, P. (1974) Synaptic termination of afferents from the ventrolateral nucleus of the thalamus in the cat motor cortex. A light and electron microscope study. *Journal of Comparative Neurology*, **153**, 77-106.

VOGT, B. A. and PANDYA, D. N. (1978) Cortico-cortical connections of somatic sensory cortex (areas 3, 1 and 2) in the Rhesus monkey. *Journal of Comparative Neurology*, **177**, 179-192.

WELT, C., ASCHOFF, J. C., KAMEDA, K. and BROOKS, V. B. (1967) Intracortical organization of cat's motosensory neurons. In: *Symposium on Neurophysiological Basis of Normal and Abnormal Motor Activities*. Edited by D. P. Purpura and M. D. Yahr. New York: Raven Press, pp. 255-293.

WIITANEN, J. T. (1969) Selective silver impregnation of degenerating axons and axon terminals in the central nervous system of the monkey (*Macaca mulatta*). *Brain Research, Amsterdam*, **14**, 546-548.

WINFIELD, D. A. and POWELL, T. P. S. (1976) The termination of thalamocortical fibres in the visual cortex of the cat. *Journal of Neurocytology*, **5**, 269-281.

YOSHIDA, M., YAJIMA, K. and UNO, M. (1966) Different activation of the 2 types of the pyramidal tract neurons through the cerebello-thalamocortical pathway. *Experientia*, **22**, 331-332.

(*Received April 20, 1978*)

Brain (1978), **101**, 543–553

AN ELECTRON MICROSCOPIC STUDY OF THE TERMINATION OF INTRACORTICAL AXONS UPON BETZ CELLS IN AREA 4 OF THE MONKEY

by K. C. GATTER, J. J. SLOPER *and* T. P. S. POWELL

(*From the Department of Human Anatomy, South Parks Road, Oxford*)

INTRODUCTION

IN the preceding paper (Gatter and Powell, 1978) a description was given of the pattern of degeneration seen with the light microscope surrounding small lesions in the motor cortex. A prominent feature was a plexus of degenerating horizontal fibres in layer IV and the upper part of layer V which extended for a few millimetres and which was asymmetrically distributed, being longer anteroposteriorly than mediolaterally. The constituent fibres were closely related to the Betz cells with degenerating fragments in close proximity to the cell somata. In sections of human motor cortex prepared by the Golgi technique a plexus of horizontal axons has been described in layer IV and the upper part of layer V which is similarly more extensive anteroposteriorly than mediolaterally. The axons of this plexus arise from stellate cells and terminate in dense pericellular baskets around pyramidal cell somata, and particularly of Betz cells (Cajal, 1911; Marin-Padilla, 1969, 1970). These observations suggest that the fibres make axo-somatic synapses on to Betz cells and this question has now been investigated using the electron microscope.

MATERIAL AND METHODS

Under Nembutal anæsthesia and with aseptic precautions the precentral gyrus of the left hemisphere was exposed in one monkey. By inserting a needle at three points on the lateral surface of the gyrus separated by approximately 1 cm from each other, lesions were made through the depth of the cortex. These lesions were comparable with the largest type used in the light microscopical study. After a survival period of two days the animal was again anæsthetized, cooled to 25° C and perfused through the heart with glutaraldehyde 1 per cent and formaldehyde 4 per cent following a brief washout with buffered saline. The brain was removed and immersed in fixative at 4° C.

The lesions were identified on the fixed brain and a block of cortex including each lesion was removed. The blocks were cut into 1 mm thick slices perpendicular to the pia and extending through the full depth of the cortex. Each slice contained part of the lesion with approximately 2 to 3 mm of cortex on either side of it. The slices were rinsed briefly in 10 per cent sucrose in phosphate buffer, transferred to 2 per cent osmic acid before being dehydrated through graded alcohols (including block staining with uranyl acetate at the 70 per cent alcohol stage) and embedded in Epon-Araldite. One μm 'thick' sections for light microscopy were cut from the long face of the block perpendicular to the pia, and stained with a mixture of methylene blue and Azure II (Richardson, Jarrett and Finke, 1960). The lesion and the Betz cells in layer V could be clearly identified in these sections (fig. 1A). Betz cells between 0·5 and 2·5 mm from the lesion were selected and a mesa of approximately 1·5 mm × 0·5 mm was trimmed to include the deep part of layer III, layer IV and the upper part of layer V. Serial ultrathin sections were cut, mounted on formvar-coated 1 mm × 2 mm single hole grids and stained with uranyl acetate and lead citrate. The somata of the chosen Betz cells were then studied for the presence of degenerating axon terminals making synaptic contacts upon them.

RESULTS

In the light microscopic study the dense degeneration around a lesion was found to be restricted to about 0·25 mm in either direction whereas the degeneration in the fibre plexus in layer IV and the upper part of layer V extended for 2 to 3 mm. Betz cell somata were studied between 0·5 and 2·5 mm from the lesion, well beyond the dense degeneration and where there was only an occasional degenerating axon terminal, most of which made asymmetric synapses on to spines (fig. 1B and C). Several degenerating myelinated axons were present and the majority were disposed horizontally. The neuropil in this region was well preserved and similar to that seen in normal material.

Betz cells identified in the thick sections could be recognized in serial ultrathin sections by their size and position, and in some cases it was possible to confirm their relationship to the lesion directly in the ultrathin sections when they were close enough for the edge of the damage to be included in the section (fig. 2A). Degenerating axon terminals were found making synapses on to most of the Betz cell somata even though the cells were only followed through ten to twenty serial sections (figs. 2 and 3). These terminals showed the typical dark type of degeneration found in the neocortex and various stages of degeneration from early to late were present; the type of membrane specialization of the synapses made by these degenerating terminals was always of the symmetrical type. Some of the Betz cells received synapses from more than one degenerating terminal in a single section (fig. 2). One Betz cell was found in which the whole length of its axon initial segment and the first part of its myelinated axon were cut in continuity in a single section and in an adjoining section a degenerating terminal made a symmetrical synapse on to the initial segment close to its origin (fig. 4). Degenerating axon terminals making symmetrical synapses were also found upon the proximal parts of apical dendrites of the Betz cells. Although up to three degenerating terminals were found to make synapses on to a single Betz cell in a small number of serial sections, the majority of the axo-somatic synapses on these Betz cells were normal (fig. 1D). However, the degenerating terminals represented a considerable proportion of the synapses received by the somata and proximal processes of these Betz cells, far higher than the proportion of degenerating terminals in the neuropil surrounding these cells.

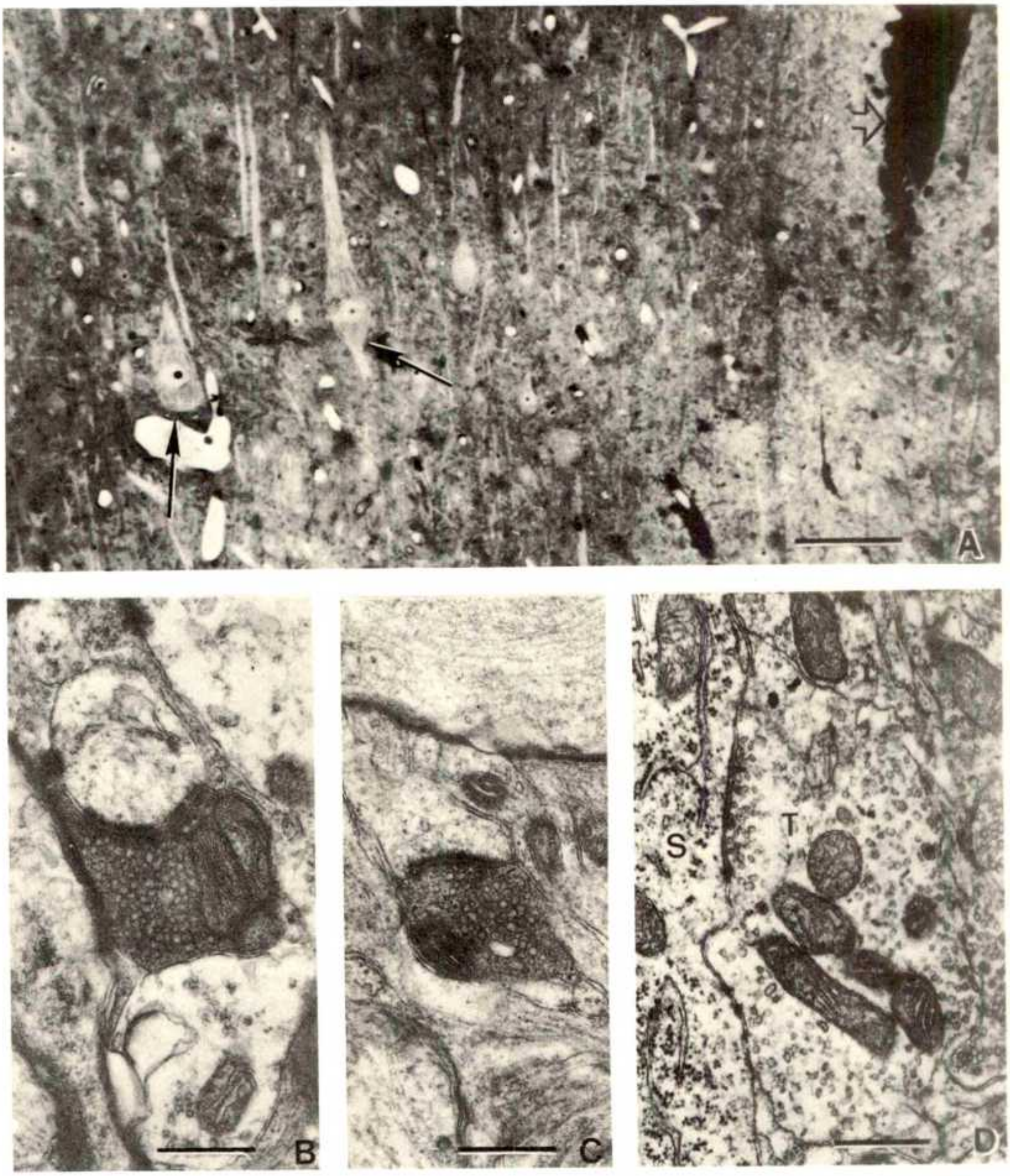


FIG. 1. A, Photomicrograph of a 'thick' section to show the relationship of two of the Betz cells (thin arrows) to the lesion (top right-hand corner—'open' arrow). Bar = 100 μm. B, C, Typical degenerating terminals making asymmetrical synapses seen in the neuropil of layer IV. Both Bars = 0·5 μm. D, A normal terminal (T) making a symmetrical synapse on to the soma (S) of a Betz cell. Bar = 0·5 μm. Abbreviations: D = dendrite of Betz cell. H = axon hillock of Betz cell. S = soma of Betz cell. T = axon terminal.

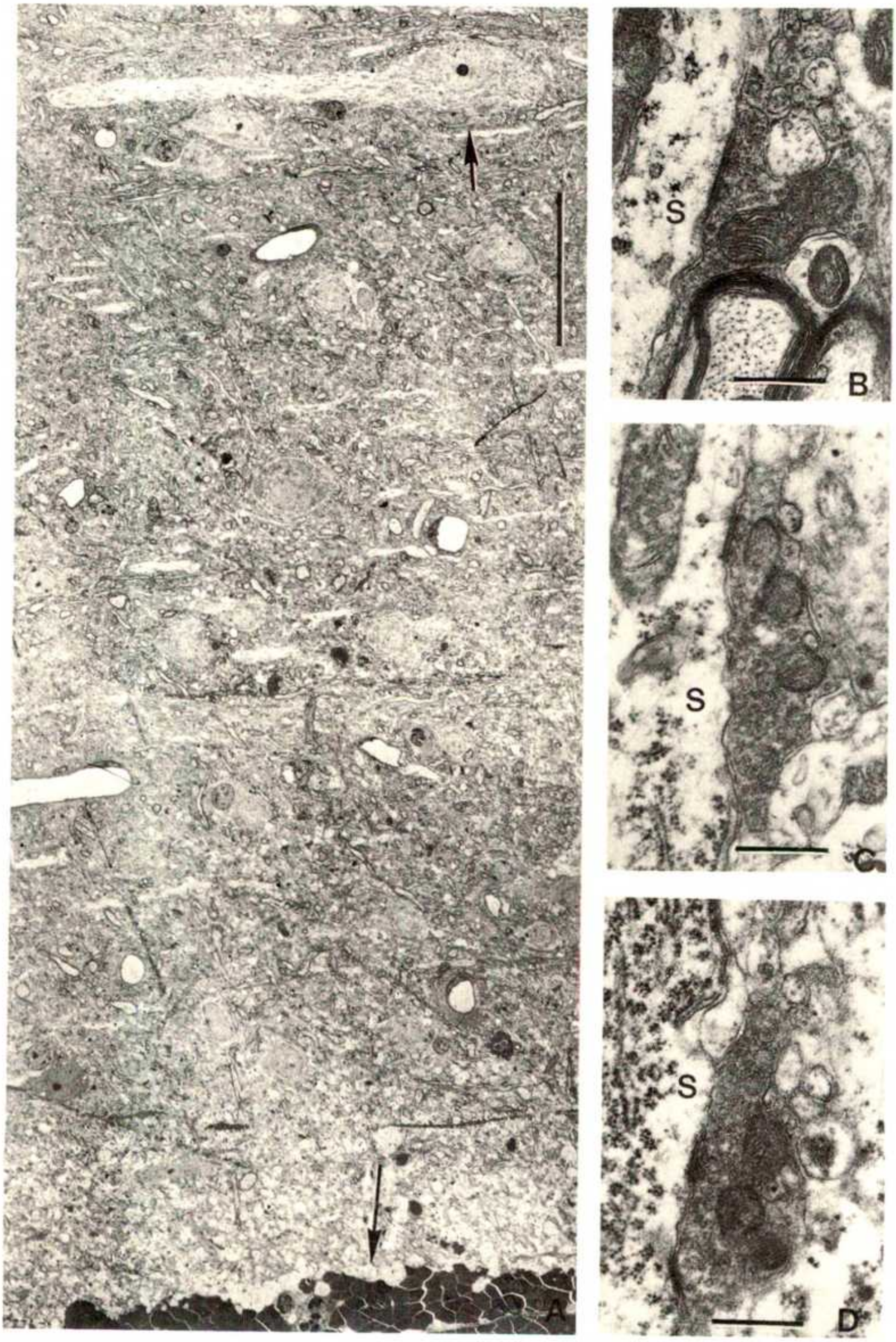


FIG. 2. A, Electron micrograph showing the relationship of a Betz cell (short arrow) studied to the lesion (long arrow). It should be noted that the superficial margin of the cortex is to the left and the deep aspect to the right. Bar = 50 μm. B, C, D, Three examples of early degenerating terminals making symmetrical synapses on to the soma of the Betz cell arrowed in A. All Bars = 0·5 μm. For abbreviations *see* fig. 1.

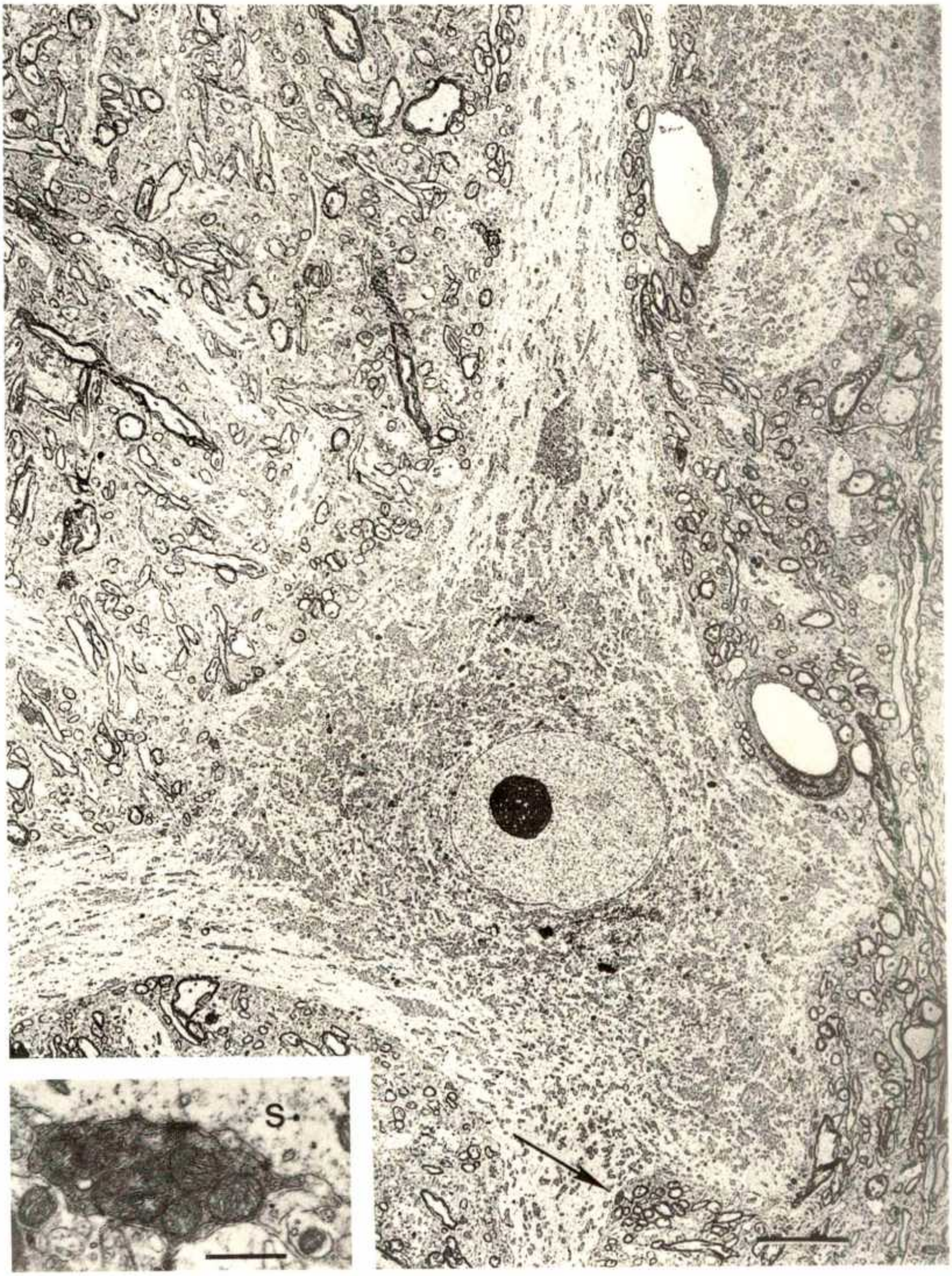


FIG. 3. A typical Betz cell approximately 2 mm from a lesion bearing a degenerating dark terminal (arrow) at the junction of a basal dendrite with the cell somata. Bar = 10 μm. *Inset*, A higher power view of the degenerating terminal to show the symmetrical synapse. Bar = 0·5 μm. For abbreviations *see* fig. 1.

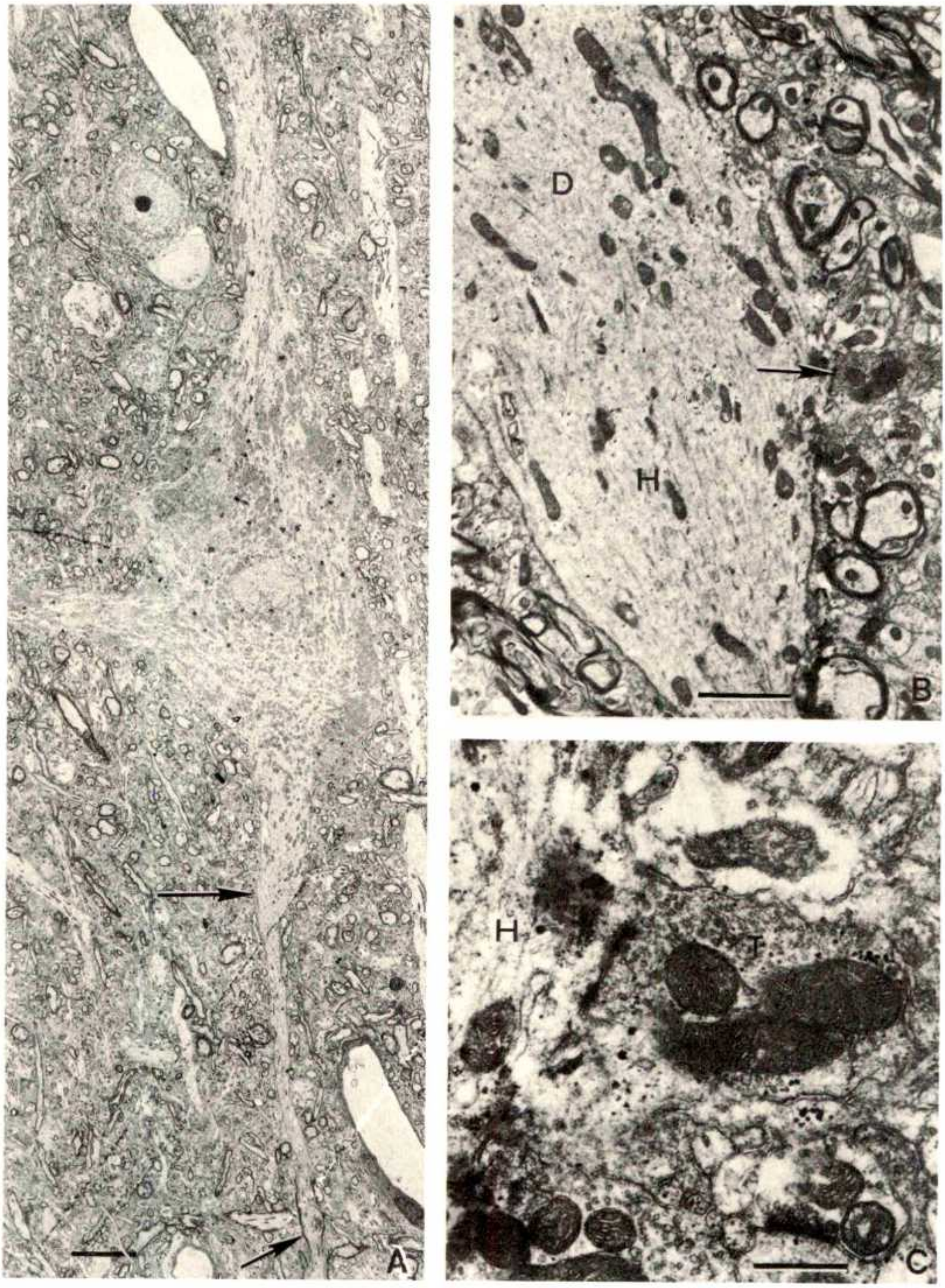


FIG. 4. A, Betz cell in which the apical dendrite, soma and axon were all cut in the same section. The axon initial segment is seen to arise from a basal dendrite (long arrow) and to become myelinated in the same section (short arrow). Bar = 10 μm. B, In an adjoining serial section to A, a degenerating terminal (arrow) makes a symmetrical synapse upon the axon hillock (H) just beyond its origin from a basal dendrite (D). Bar = 2 μm. C, Higher power view of the degenerating terminal (T) in B to show the symmetrical membrane thickenings of the synapse. Bar = 0·5 μm. For abbreviations *see* fig. 1.

DISCUSSION

In material prepared by the Golgi technique a plexus of horizontal fibres orientated mainly in the anteroposterior dimension has been described in layers IV and V of the human motor cortex (Marin-Padilla, 1969, 1970) and the axons arise from stellate cells in these layers and end as pericellular baskets around the somata and proximal processes of pyramidal cells. By analogy with the similar basket arborizations around Purkinje cell somata in the cerebellum and pyramidal cell somata in the hippocampus it seemed probable that the axons of these pericellular baskets in the neocortex make synapses on to the somata and proximal processes of pyramidal cells (Marin-Padilla, 1969, 1970). The present electron microscopic evidence of degenerating terminals making symmetrical synapses upon the somata, apical dendrites and initial segments of Betz cells 1·0 to 1·25 mm from the lesion therefore supports the conclusions drawn from light microscopy and suggests that these synapses form a major termination of this plexus because there were few degenerating axons in the neuropil surrounding them. As the synapses on the somata and proximal processes of Betz cells are likely to have a powerful influence on the activity of these cells, identification of their cells of origin is of considerable interest. Previous studies have shown that symmetrical synapses persist after undercutting the cortex (Szentágothai, 1964; Gruner, Hirsch and Sotelo, 1974) and no symmetrical axon terminals have been shown to degenerate after lesions of afferent projections to the motor cortex (Sloper, 1973; Strick and Sterling, 1974), so it has been concluded that symmetrical axon terminals arise from neurons within the cortex. The horizontal plexus in layers IV and V does not degenerate after lesions deep to layer V (Gatter and Powell, 1978) showing that it consists of axons intrinsic to the cortex. Slight degeneration of these axons occurred after damage of the superficial layers of the cortex but only when the deep part of layer III and layer IV were involved was heavy degeneration of this band seen. The basket cell axons have the greatest horizontal spread of any cell type in the neocortex and the degenerating axon plexus in layer IV also extends the furthest after intracortical lesions. There is therefore good agreement between experimental studies and observations on Golgi-impregnated material that the axo-somatic synapses on Betz cell somata arise from an interneuron, the basket cell, that is found in layer IV and the adjacent parts of layers III and V and whose axons run in a plexus at the same level.

On the basis of close similarities of several morphological features and of laminar distribution it has been suggested that the basket cell corresponds to the large stellate cell of electron microscopy (Sloper, Hiorns and Powell, 1978). The terminals of thalamic, commissural and association afferent fibres to the motor cortex make asymmetric synapses, and a small proportion of fibres of each of these pathways end upon the somata and dendrites of large stellate cells while the majority terminate upon dendritic spines which probably arise from dendrites of pyramidal cells (Sloper, 1973; Strick and Sterling, 1974). Stimulation of the ventrolateral nucleus of the thalamus (Amassian and Weiner, 1966) and of the contralateral motor cortex (Asanuma and Okuda, 1962) result in monosynaptic excitation of physiologically identified corticospinal cells and thalamic stimulation also excites interneurons (Stefanis, 1969; Stone, 1973). This excitatory effect upon the pyramidal cell is followed by a long lasting inhibition. From a synthesis of these anatomical and physiological findings it may therefore be suggested that the asymmetrical terminals of these afferent fibres excite both types of cells monosynaptically and that the delayed inhibition in adjoining pyramidal cells is mediated disynaptically through the large stellate/basket cell, its axon making symmetrical type synapses which have been correlated with inhibition elsewhere (Uchizono, 1965).

Stimulation of the corticospinal axons in the brain stem also causes an excitatory-inhibitory sequence of activation of pyramidal cells and excitation of nonpyramidal tract neurons (Phillips, 1956, 1959; Stefanis and Jasper, 1964*a*, *b*; Brooks and Asanuma, 1965). These effects are most probably due to the activation of recurrent axon collaterals within the cortex, the early excitatory effect through direct synapses upon the dendrites of pyramidal cells and the pronounced and longer lasting inhibition through an inhibitory interneuron whose axon terminates 'close to the spike generating area' (Stefanis and Jasper, 1964*b*). As there is electron microscopic evidence that axon collaterals of pyramidal cells make synaptic contacts with the dendrites of large stellate neurons (Sloper and Powell, 1978), it would seem that this cell is responsible for the inhibitory effect. Further support for this correlation is that the nonpyramidal tract cells or interneurons excited by pyramidal tract stimulation are also monosynaptically activated by thalamic stimulation, and the majority are situated about the same depth and in close proximity to the large pyramidal tract cells (Stefanis, 1969; Stone, 1973). There is therefore anatomical and physiological evidence for convergence of extrinsic afferent and recurrent axon collaterals on to an interneuron which probably has an inhibitory effect upon pyramidal tract cells.

In the preceding paper the anatomical findings were discussed in relation to the input-output column which has been described in functional studies. Some of the degenerating fragments extending over a few millimetres in all layers are probably of axons which are excitatory, but if those in the dense plexus in layer IV arise from the basket/large stellate cell and inhibit Betz and other pyramidal cells, they could be an important mechanism for surround or pericolumnar inhibition (Brooks, Rudomin and Slayman, 1961; Stefanis and Jasper, 1964*b*). As the large stellate cell receives afferent and recurrent collateral fibres *it may inhibit surrounding cells in relation to both the input and output activities*, and because the thalamic afferent and recurrent collateral axons may branch over 3 mm before a further spread of similar extent by the basket cell axons, the total distance affected could be several millimetres in all directions. This would be in accord with the observations of Asanuma and Okuda (1962) that an excitatory response to commissural fibre activation was found only upon stimulation of a precise and restricted area of the

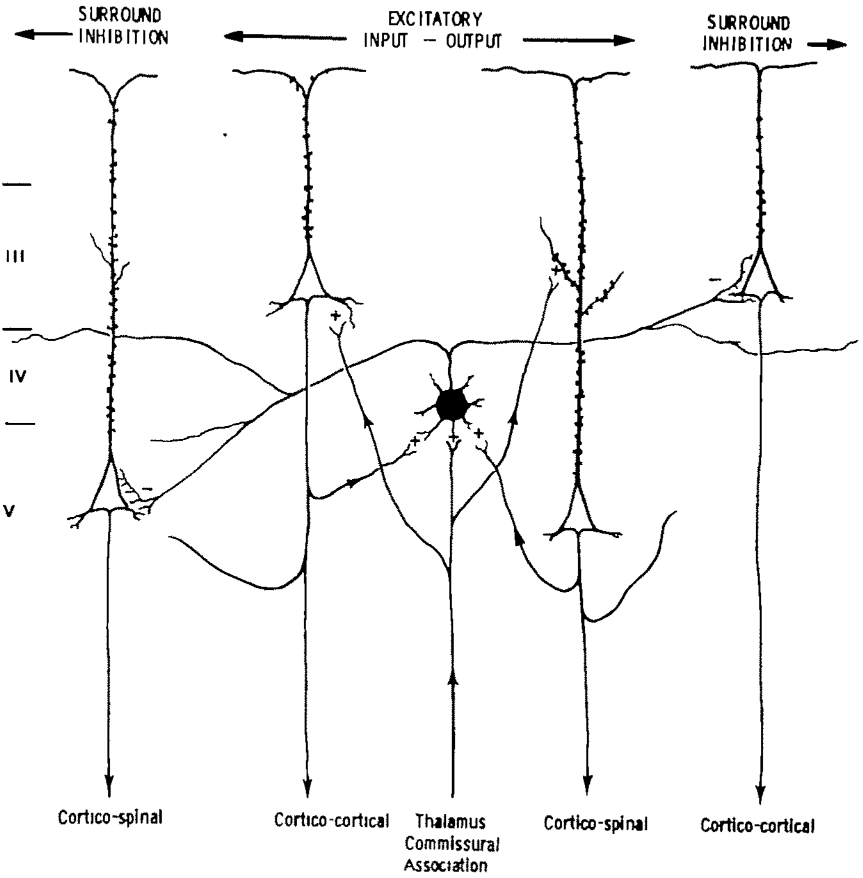


FIG 5. A schematic figure to show the connections and their functional excitatory or inhibitory influences based upon the collation of the results of light and electron microscopic studies of experimental and Golgi-impregnated material, together with the findings in electrophysiological investigations. The filled neuron in layer IV with horizontally disposed axonal branches is the basket cell described in Golgi material and which has an inhibitory effect upon adjoining pyramidal cells in the deep part of layer III and the Betz cells in layer V

cortex whereas inhibition resulted from stimulation of a much wider area surrounding the site from which excitation was obtained.

Following small lesions in area 17 of the monkey visual cortex a horizontal plexus of degenerating axons is found in the stria of Gennari (Fisken, Garey and Powell, 1975) and in many respects it is similar to that in the motor cortex: the fibres are relatively large with the greatest horizontal spread of degeneration, they arise within the cortex, mainly from layer IV, and they terminate in close relationship with cells in layer III where large pyramids predominate. The electron microscopic part of the study of Fisken *et al.* (1975) gave an overall view of the degeneration surrounding a small cortical lesion rather than concentrating on a particular aspect, but a greater proportion of degenerating axon terminals which made symmetrical synapses were found at increasing distances from the lesion.

SUMMARY

After small lesions within the cortex of area 4 of the monkey degenerating axon terminals have been seen with the electron microscope to contact the cell bodies, proximal parts of the apical dendrites and initial segments of Betz cells 0·5 to 2·5 mm from the damage. The degenerating axon terminals make symmetrical synapses which are presumed to be inhibitory in function. The degenerating terminals are probably from the axons of the basket cells described in Golgi-impregnated material, and which correspond to the large stellate cell recognized in electron microscopic studies.

ACKNOWLEDGEMENTS

This work was carried out with the aid of grants from the Medical and Science Research Councils and the Wellcome Trust.

REFERENCES

AMASSIAN, V. E. and WEINER, H. (1966) Monosynaptic and polysynaptic activation of pyramidal tract neurons by thalamic stimulation. In: *The Thalamus*. Edited by D. P. Purpura and M. D. Yahr. New York and London: Columbia University Press, pp. 255–282.

ASANUMA, H. and OKUDA, O. (1962) Effects of transcallosal volleys on pyramidal tract cell activity of cat. *Journal of Neurophysiology*, **25**, 198–208.

BROOKS, V B. and ASANUMA, H. (1965) Recurrent cortical effects following stimulation of medullary pyramid. *Archives Italiennes de Biologie*, **103**, 247–278.

—— RUDOMIN, P. and SLAYMAN, C. L. (1961) Peripheral receptive fields of neurons in the cat's cerebral cortex. *Journal of Neurophysiology*, **24**, 302–325.

CAJAL, S. R. y. (1911) Histologie du Système nerveux de l'Homme et des Vetébrés. Vol. II. Paris: Maloine.

FISKEN, R. A., GAREY, L. J. and POWELL, T. P S. (1975) The intrinsic, association and commissural connections of area 17 of the visual cortex. *Philosophical Transactions of the Royal Society*, B, **272**, 487–536.

GATTER, K. C. and POWELL, T. P. S. (1978) The intrinsic connections of the cortex of area 4 of the monkey. *Brain*, **101**, 513–541.

GRUNER, J. E., HIRSCH, J. C. and SOTELO, C. (1974) Ultrastructural features of the isolated suprasylvian gyrus in the cat. *Journal of Comparative Neurology*, **154**, 1–28.

MARIN-PADILLA, M. (1969) Origin of the pericellular baskets of the human motor cortex: a Golgi study. *Brain Research, Amsterdam*, **14**, 633–646.

—— (1970) Prenatal and early postnatal ontogenesis of the human motor cortex: a Golgi study. 2. The basket-pyramidal system. *Brain Research, Amsterdam*, **23**, 185–191.

PHILLIPS, C. G. (1956) Intracellular records from Betz cells in the cat. *Quarterly Journal of Experimental Physiology*, **41**, 58-69.

—— (1959) Actions of antidromic pyramidal volleys on single Betz cells in the cat. *Quarterly Journal of Experimental Physiology*, **44**, 1-25.

RICHARDSON, K. C., JARRETT, L. and FINKE, E. H (1960) Embedding in epoxy resins for ultrathin sectioning in electron microscopy. *Stain Technology*, **35**, 313-323.

SLOPER, J. J. (1973) An electron microscope study of the termination of afferent connections to the primate motor cortex. *Journal of Neurocytology*, **2**, 361-368.

—— HIORNS, R. W. and POWELL, T. P. S. (1978) A qualitative and quantitative electron microscopic study of the neurons in the primate motor and somatic sensory cortices. *Philosophical Transactions of the Royal Society*, Series B. (in press).

—— and POWELL, T. P. S. (1978) A study of the axon initial segment and proximal axon of neurons in the primate motor and somatic sensory cortices. *Philosophical Transactions of the Royal Society*, Series B. (in press).

STEFANIS, C. (1969) Interneuronal mechanisms in the cortex. In: *The Interneuron*. Edited by M. A. B. Brazier. Berkeley and Los Angeles: University of California Press, pp. 497-526.

—— and JASPER, H. (1964*a*) Intracellular microelectrode studies of antidromic responses in cortical pyramidal tract neurones. *Journal of Neurophysiology*, **27**, 828-854.

—— —— (1964*b*) Recurrent collateral inhibition in pyramidal tract neurones. *Journal of Neurophysiology*, **27**, 855-877.

STONE, T. W. (1973) Cortical pyramidal tract interneurones and their sensitivity to L-glutamic acid. *Journal of Physiology, London*, **233**, 211-225.

STRICK, P. L. and STERLING, P. (1974) Synaptic termination of afferents from the ventrolateral nucleus of the thalamus in the cat motor cortex. A light and electron microscope study. *Journal of Comparative Neurology*, **153**, 77-106.

SZENTÁGOTHAI, J. (1964) The use of degeneration methods in investigation of short neuronal connections. *Progress in Brain Research*, **14**, 1-30.

UCHIZONO, K. (1965) Characteristics of excitatory and inhibitory synapses in the central nervous system of the cat. *Nature, London*, **207**, 642-643.

(*Received April 20, 1978*)

Brain (1978), **101**, 555-568

NOTICES OF RECENT PUBLICATIONS

Corticospinal Neurones. Their Role in Movement. By C. G. PHILLIPS and R. PORTER. 1977. Pp. 450. London: Academic Press. Price £16.80.

More than seventy years ago Sherrington (1906) expressed his belief that by a combination of the methods of psychology and experimental physiology 'investigations may be expected ere long to furnish new data of importance toward the knowledge of movement as an outcome of the working of the brain'. In their work on *Corticospinal Neurones*, Phillips and Porter have assembled data showing that Sherrington's hope has at last been realised. In this monograph for the Physiological Society the authors have gone far beyond a consideration of the role of corticospinal neurons in any narrow sense, for in seeking to analyse the role of corticospinal neurons as a major efferent pathway from the brain they have been led to consider both the higher and the lower level structures with which corticospinal neurons interact. Their task, as they set it forth at the outset, was to reassess the status of the pyramidal tract: '(1) as a 'common' or 'internuncial path' projecting the commands of the central programmes and subroutines towards the target muscles; (2) as a source of internal feedback (*efference copy, corollary discharge*) to the central programme, informing it of the progress of the subroutines of performance; (3) as a controller of the gain and discrimination of afferent systems supplying information to the fore-brain and cerebellum; and (4) as the efferent limb of transcortical reflex arcs whose afferent limbs may provide feedback control of the subroutines'.

Considerable attention is devoted to the comparative anatomy and the comparative physiology of corticospinal neurons, since so much can be learned from phylogenetic adaptations in the patterns of termination of corticospinal neurons according to the functional requirements of the motor systems which they control. For example, the authors cite evidence that in man there are dense endings of pyramidal tract neurons (PTNs) in the thoracic cord in regions containing motoneurons innervating respiratory muscles. It might at first seem odd that phylogenetically new corticospinal neurons should terminate on motoneurons controlling muscles which participate in an act as automatic and primitive as respiration, but as the authors point out, these terminations are probably related to use of respiratory muscles not in breathing but in speech and song: the corticospinal projection provides for control of old muscles in new patterns, and as Hughlings Jackson recognized so clearly, loss of the corticospinal projection does not paralyse muscles *per se*, but eliminates their use in the context of certain movements. Destruction of the corticospinal projection to thoracic motoneurons does not impair the utilization of respiratory muscles in the context of respiration, though these same muscles may be useless in the context of speech.

The preceding statement concerning muscles and movements touches on an issue which has been much discussed in scientific works on the organization of the motor cortex, and this in turn is an issue which the monograph of Phillips and Porter has succeeded in clarifying. Elsewhere, Phillips (1975) had dealt with this issue in a paper entitled 'Laying the ghost of 'muscles versus movements'.' In introducing his discussion of this topic, Phillips stated: 'The ghost I am raising is the ghost of what I think should never have been regarded as a live issue: whether 'muscles' or 'movements' are 'represented' in the sensorimotor cortex. It walked the corridors of neurology in the nineteen-thirties and -forties and then seemed, in the nineteen-sixties, to be fading quietly away, losing its hold over a new generation of microanatomical and microphysiological researchers who were busying themselves with details of corticospinal connectivity. . . . It had depended all along for its influence on spreading the false belief that a man called Hughlings Jackson had formulated alternative propositions, 'muscles' or 'movements', A or B; and on suggesting that one or other of these propositions could, in principle, be demolished by a suitable experiment: one involving electrical stimulation of the cortex. Jackson had, in fact, propounded no such alternatives'.

Much light has been shed on this issue by the work of Phillips and a number of his associates, and out of this work has come the concept of the 'corticomotoneuronal colony', a term referring to that collection of corticospinal tract (CST) neurons which project monosynaptically to a single spinal cord motoneuron. The experiments revealing the extent of corticomotoneuronal colonies involved intracellular recording of monosynaptic EPSPs from spinal cord motoneurons. After a given spinal cord motoneuron had been impaled with the intracellular microelectrode, the motor cortex surface was mapped with a roving focal anode delivering pulses which were near threshold for the direct excitation of CST axons, so that the maps were subjected to little error due to physical spread of current or physiological spread of excitation. It was found that the projection area to a single motoneuron could be extensive (up to 13 mm square), that areas were sometimes multiple, and that a colony for a given motoneuron commonly overlapped with colonies projecting to motoneurons of antagonistic as well as synergistic muscles.

It is worth reiterating that the extent of a given corticomotoneuronal colony was defined by projections from cerebral cortex to a *single motoneuron*. If one now thinks of the region enclosing the *set of corticomotoneuronal colonies* projecting to *all the motoneurons* of a given muscle, one realises that it is a region which must indeed be extensive and must of necessity overlap with regions projecting to motoneurons of other muscles—both agonists and antagonists.

Just as Phillips and his colleagues have succeeded in laying to rest the argument of 'muscles versus movements', they have also laid to rest an idea which for a time seemed to be emerging from results of motor cortex microstimulation, and they conclude that 'there is no experimental basis for any suggestion that the motor cortex might be built up of isolated cylindrical output columns of equal radius, one for every muscle in the body' (p. 204).

Coupled with this lucid consideration of motor cortex output is an equally clear consideration of the inputs to PTNs. Two major categories were considered: inputs conveying programs from higher functional levels and inputs relaying feedback from lower levels. In the program category were included signals from neocortex, lateral cerebellum, basal ganglia, and the ventrolateral thalamus. In the feedback category 'the signals ascending to the motor cortex would be mainly, if not exclusively, aroused as responses to its own projected activity. They can be classified as *internal feedback*, arising in the intermediate region of the cerebellum, in sensory relay nuclei, as patterned responses to the patterned discharges of PT impulses, and *external feedback*, originating in the muscles, joints and skin of the moving parts' (p. 205).

In discussing the cortical organization whereby these two classes of inputs generate motor cortex outputs, the authors focus on the radial input-output architecture of the motor cortex. It should be noted that the existence of a radial architecture does not imply the existence of functionally isolated cylindrical output columns. Thus, radial architecture is a histological fact, but this fact does not provide evidence for or against a columnar organization.

The cerebellum participates in generating both of the major categories of input which reach the motor cortex (both the programs and the feedback), and the authors differentiate between the role of that cerebellar projection reaching motor cortex from dentate as compared to the projection from the interpositus nucleus. The dentate, driven by the lateral cerebellum, is thought of in relation to motor programs arising from internal sources, whereas the interpositus is thought of in relation to feedback generated in the course of movement. It is pointed out that 'If it could be proved that nucleus interpositus is, in fact, a *relay* nucleus, this would have great theoretical interest which cannot be allowed to pass without comment. The deep cerebellar nuclei are analogous to the vestibular nuclei in that they receive excitatory inputs from outside the cerebellum, and are subject to inhibition by the cerebellar Purkinje cells. Thus transmission through nucleus interpositus would be inhibited by the cortex of the intermediate region, as transmission through the vestibular nuclei is inhibited by the cortex of the flocculonodular lobe. One of the vestibular nuclei contains the second-order neurones of the vestibulo-ocular reflex and the cortex of the flocculonodular lobe receives a parallel afferent input of mossy fibres from the vestibular apparatus. When the normal relationship between the directions of rotation of the head and of the visual field is artificially reversed, the vestibulo-ocular reflex undergoes an appropriate 'plastic' change; and there is evidence that this change depends on a modification of the inhibitory action of the cortex on the nucleus.

'The cortex of the intermediate region receives information of length, rate of change of length, and tension of the muscles. So if nucleus interpositus is actually responsible for transmission of signals of muscle length (from spindle secondaries) and tension (from Golgi tendon organs) to the motor cortex, there would be interesting possibilities of cerebellar modification of their actions on its output, whether by short-term 'switching' or by long-term 'plastic' change' (p. 226).

The authors' suggestion along these lines is indeed an important one. Much current work on the vestibulo-ocular reflex (VOR) is aimed at elucidating mechanisms underlying VOR plasticity. Sherrington viewed the labyrinthine and muscle afferents as the two great sources of proprioceptive inputs. It might be anticipated that mechanisms underlying plasticity of the VOR might apply to plasticity in proprioceptive reflexes affecting output of cerebral motor cortex.

Having dealt definitively with the input-output organization of motor cortex, the authors proceed to a chapter which integrates this knowledge with currently available information on the 'Electrophysiology of Neurones of Cortical Projection Areas in Relation to Conditioned and Voluntary Movement.' There are now extensive data concerning the activity of PTNs during voluntary movement, and these data fit beautifully with the ideas of motor cortex organization which Phillips and his colleagues have put forward on the basis of their electrophysiological work. It is indeed in this chapter on movement that Phillips and Porter bring us to the fruition of the line of thinking which began with ideas of Jackson and Sherrington, progressed through the elegant intracellular electrophysiological studies of Phillips, and led to studies of PTN activity in moving animals. As already mentioned, the work of Phillips and his colleagues had shown that corticomotoneuronal colonies may occupy many square millimetres. Such a finding, coupled with the demonstrated overlap of corticomotoneuronal colonies to motoneurons of different muscles, implied that during natural voluntary movement a microelectrode which simultaneously registered the action potentials of two adjacent PTNs might show that PTNs which are 'geographical neighbours' can be 'physiological antagonists'. This would be expected for PTNs from overlapping corticomotoneuronal colonies to motoneurons of muscles which were reciprocally related for the movement in question: the demonstration of overlapping corticomotoneuronal colonies of agonist and antagonist motoneurons implied that representative PTNs of these colonies would be reciprocally related. Demonstrations of such PTN reciprocity in natural movement have now been made.

Studies of PTN activity in the course of natural movement have been an area of special contribution by Porter, who first collaborated with Phillips in carrying out electrophysiological investigations in cortex and spinal cord—and then extended his work to include studies of extracellular discharges of single PTNs during natural movements of the primate. One of the major points of satisfaction emerging from this line of work is the way in which the results on natural movement fit with and extend the general notions which had already evolved through the last two decades of work by Phillips and his numerous colleagues. For example, Phillips proposed that the PTN input-output modules of the cerebral motor cortex might provide a transcortical reflex mechanism allowing for the continuous and automatic regulation of skilled volitional movement. In the early studies on activity of motor cortex neurons in relation to voluntary movement it was observed that PTNs discharged prior to movement, and the PTN output was viewed as a command signal which would specify some peripheral event. Little attention was given to the altered feedback that might continuously influence this PTN activity during movement until Phillips proposed that the changes in PTN activity during movements with different loads might be the result of feedback. According to Phillips' hypothesis, PTN output might represent a mismatch between actual and intended movement. Phillips' suggestion that we view the PTN as a summing point in a transcortical servo loop allowed us to interpret increased pyramidal tract discharge with increased loads as an error signal corresponding to a mismatch between intended and actual displacement. The

Phillips hypothesis has since been extensively confirmed in studies of PTN discharge in moving monkeys, and it has been found that the output of many PTNs does in fact represent a signal indicating mismatch between intended and actual movement. Here then, one has the clear meeting of experimental psychology and physiology. Sherrington's discoveries on reflex action at the level of the spinal cord made it clear that the spinal cord alpha motoneuron was a summing point for peripheral feedback and central programs from a number of CNS loci. We now know that a similar interaction between peripheral feedback and central programs occurs at the level of the cerebral motor cortex Of course the pathways for feedback and the origin of the central programs are different in the two cases. The spinal cord represents a lower level and the cerebral motor cortex a middle level in the hierarchical organization proposed by Hughlings Jackson. For the spinal cord motoneurons, the central program descends while the feedback comes directly from segmental afferent inputs. For the motor cortex, the central programs appear to be relayed via the thalamus, and somæsthetic feedback appears to be relayed predominantly via sensory receiving areas adjacent to the motor cortex. But the general principles are the same.

The demonstration that the motor cortex, a zone of critical importance in voluntary movement, is also a site for reflex action was in fact predicted long ago. Jackson had expressed the view that highest cerebral centres involved 'sensorimotor processes', representing the parts of the body as certainly as the lumbar enlargement does. Phillips and Porter point out that by sensorimotor processes Jackson 'implied the idea, which he had taken from Laycock, that the brain is subject to the laws of reflex action' (p. 323). As cited by Phillips and Porter, Jackson went on to say that 'In the lower centres there is a direct adjustment of few and simple movements to few and simple peripheral impressions. In the very highest centres also there is a similar adjustment, but then it is of exceedingly special movements (representing movements of the whole organism) to the most special impressions from the environment . . . In the lower reflex action some particular movement is fatally necessary and occurs rapidly after some particular impression. But in the highest centres it may be that there is not this absolute connexion . . . the sensory and motor elements which enter into the physical side of what is, psychologically speaking, our perception of the statical and dynamical qualities of objects, can be, so to speak, transposed, can enter into new combinations' (p. 323).

One is struck at the prescience of Jackson and Laycock, whose ideas are dealt with so fully in *Corticospinal Neurones*. But Phillips and Porter do not restrict themselves to reviewing the ideas of the British school. Indeed, there are excellent reviews of the ideas of Nicholas Bernstein and of Lashley. Phillips and Porter were much impressed with Bernstein's original and highly logical formulations. It seems clear that as Western neurophysiologists become more familiar with Bernstein's work, this work will have a greater and greater impact on their ideas. Westerners sometimes think that ideas concerning movement in the Soviet Union derive largely from the school of Pavlov, but as readers of the Phillips and Porter book will come to realise, the ideas of Nicholas Bernstein are quite different. The treatment given to Bernstein's ideas in the present volume will surely stimulate the reader to delve more deeply into the work of the Russian school—a group having its origins in mathematics, cybernetics, and kinesiology. Bernstein died in 1966, but the school which he founded is active in Moscow, and its members are providing some of the most important current work concerning organization of movement.

In addition to considering the cybernetics of movement, the authors review neuropsychological and electromyographic studies in man, and devote considerable attention to the concept of alpha-gamma linkage as this concept has been developed following the ideas of Granit and his colleagues.

Finally, there is consideration of those movements for which the corticospinal tract is most essential: speech and movements involving precise individual control of the fingers. The authors point out that 'In man, very small and accurate movements of the fingers are possible, guided by vision under the microscope. With a little practice, a person is able to position a slide accurately on the stage of a microscope using only his hand and visual control. A technician will soon find it possible to focus first on the centre of a single red blood cell viewed under high magnification, and then to move the slide so that the centre of focus is on the rim of that same erythrocyte. A delicate, controlled movement of only 3 or 4 μm has been executed with the musculature of the arms, hand and fingers. Accuracy requires external, visual feedback and the accomplishment of the precise movement performance is intimately linked with and dependent upon the sensory experience. We can also do fairly fine dissections under a dissecting microscope without recourse to a micromanipulator' (p. 378).

This reviewer was especially interested in the reference which Phillips and Porter made to the role of PTNs in precise movements, for it was with this idea in mind that I and my colleague Christoph Fromm decided to carry out observations of the activity of PTNs during small precisely-controlled movement in the monkey. In these experiments a visual pursuit-tracking paradigm was used for training monkeys to position a handle within a small zone and rotate it by pronation-supination movements. Unit discharges from the motor cortex was examined in relation to movements carried out in this situation, with particular attention to large ballistic movements as compared to small precisely controlled movements. Intense unit discharge was found to occur with even the smallest movements made to achieve accurate positioning of the handle. Within the group of motor cortex PTNs, slowly conducting tonically discharging PTNs showed the most selective relations to these small precisely controlled movements. All units discharging with small movements also discharged with larger movements, but for the larger movements there was recruitment of new PTNs which had been inactive with the small movements. Furthermore, those PTNs which were recruited with the smallest movements were also most sensitive to peripheral inputs arising from limb receptors. Almost invariably there was intense reflex activation of those units (especially the tonically discharging PTNs) most involved in control of precise small movements. Here then, in studies on individual PTNs was evidence for a very high degree of PTN involvement in the finest, most precise motor outputs, and evidence for the critical role of sensory input in precise motor output.

And, of course, Phillips and Porter stress the critical role of 'the hand as a sense organ'. Corticospinal neurons, after all, terminate in many sensory relay stations, and thus the output of the sensorimotor cortex is critical in regulation of sensory input as well as in excitation of motor output.

In closing, I must add that in attempting to review this book on *Corticospinal Neurones*, I have found it impossible to list all of the topics which have been covered. The book bridges the gap between a number of important areas—clinical neurology, neurophysiology, experimental psychology, kinesiology, and anatomy. The style is lucid and engaging, and one finds oneself drawn from chapter to chapter with avidity. Combining as it does so many different approaches to the functional organization of motor control, the book will surely be of great value as a text and a source in a number of different areas of neuroscience.

EDWARD V. EVARTS

REFERENCES

PHILLIPS, C. G (1975) Laying the ghost of 'Muscles versus Movements'. *Canadian Journal of Neurological Sciences*, 2, 209–218.

SHERRINGTON, C. (1906) *The Integrative Action of the Nervous System.* New Haven: Yale

Visual Evoked Potentials in Man: New Developments. Edited by J. E. Desmedt. 1977. Pp. 558. Oxford University Press. Price £21.00.

Visual evoked potentials refer to the voltage signals recorded from the intact scalp (usually of man) in response to appropriate visual stimulation. Experiments involving VEPs centre on the measurement of either the *transient* or *steady-state* response. In transient-VEP recording, stimuli are presented at a sufficiently low rate that the visual system may be regarded as having returned to its resting level between stimulus presentations. The response is described in terms of amplitude *vs* time and is analysed into components with different polarities and latencies. In steady-state-VEP recording, the stimulus repetition rate is sufficiently high that no individual response cycle can be associated with any particular stimulus cycle. Response is expressed in terms of amplitude and phase *vs* frequency of the (sinusoidally varying) stimulus. For a linear system, analysis of the steady-state response would be the standard method of investigation of its temporal characteristics, but the visual system is strongly nonlinear, whether evaluated by psychophysical methods (Attneave and McReynolds, 1950; Burton, 1973) or by VEP measurements (Kamp, Sem-Jacobsen, Storm van Leeuwen and Van der Tweel, 1960). The absence of any general method for nonlinear systems analysis requires the adoption of a tailor-made approach to each problem, although Spekreijse and Oosting (1970) have shown that for the case in which the visual nonlinearity may be treated as a rectifier it is possible to make use of a 'linearizing' technique. Not surprisingly, there has been little success in predicting the steady-state VEP response from the transient (Regan, 1972, p. 75).

As a technique for the investigation of human visual function, the VEP approach has several advantages over other methods. It provides an objectivity not afforded by psychophysical and neuropsychological measures and, unlike microelectrode electrophysiology involving acute preparations, it is used with the fully-conscious unanæsthetized unparalysed subject. In clinical practice, VEPs allow the assessment, in a non-injurious way, of visual function in inarticulate or unresponsive patients. VEPs have, in addition, the property that they reveal the activity not of a single cell, as in microelectrode methods, but of a group or population of cells. Nevertheless, the disadvantages of the VEP approach are not insignificant. The VEP signal has to be correlated, in some part, with an attribute of the stimulus or an aspect of the sensation elicited by the stimulus. When a statistically reliable correlation is established, it does not necessarily follow that the corresponding VEP event is directly related to the nervous activity mediating the perception of the stimulus. There are practical difficulties in that VEPs can be easily contaminated by artifacts associated with the method of stimulus presentation, and they can vary widely from person to person. There are important theoretical problems concerning the nature and distribution of the electrical processes generating these surface potentials, and the extent to which these generators reflect the structure and function of the underlying neural mechanisms. As Regan (1972, p. 26) indicates, it is this question of the relationship between nerve cells and VEPs which is the most critical for evoked potential research.

Visual Evoked Potentials in Man New Developments, edited by J. E. Desmedt, is the outcome of a project initiated at the Brussels Symposium held in April 1974 on cerebral evoked potentials and contains contributions from a leading group of VEP research workers. The book is divided into three parts. Part 1 is concerned with the basic methods of VEP stimulation and response analysis. It begins with a useful introduction to VEP terminology and procedures which is formulated by a panel consisting of Arden, Bodis-Wollner, Halliday, Jeffreys, Kulikowski, Regan and Spekreijse. There follows an excellent critical overview by Spekreijse, Estevez and Reits of VEPs in relation to visual information processing. The authors discuss VEPs elicited by homogeneous fields undergoing simple flash, sinewave and Gaussian-noise modulation, and break down the response into components deriving from different regions of the cortex. For spatially structured fields, the authors make the point that VEP responses are more complex, and there appears to be no well-defined description relating VEP characteristics to stimulus properties yet available, although it is possible to distinguish certain pattern-dependent components in the VEP response to long-duration stimuli that are present in the response to short-duration stimuli. (These components, Jeffreys' CI and CII, are discussed later in this review.) Experiments on VEPs to coloured stimuli showed that all three cone photoreceptor mechanisms yield a contrast-specific response, and, significantly, the blue-cone system requires the largest check size in the pattern. These experiments made use of what the authors called a 'spectral compensation' method in which the input to one cone system is held constant while that to another is varied. This method relates to the 'silent-exchange' technique used by Donner and Rushton (1959) in their investigation of frog retinal-ganglion-cell response. Part 1 finishes with a description by Arden and his co-workers of a versatile VEP pattern generator designed primarily for clinical work, and a review by Regan of the use of Fourier methods in steady-state VEP analysis.

Part 2 deals in detail with VEPs to pattern, colour, and eye movements in normal man. Halliday and his co-workers discuss the topography of pattern VEPs and stress the importance of the location of stimulation within the visual field in determining the nature of the response. On the basis of experiments in which the stimulus sharpness and size are varied, they hypothesize that VEPs elicited by small-check patterns involve visual 'edge-detectors' whereas those elicited by large-check patterns depend on units sensitive to areas of varying luminance. The physiological origins of pattern VEPs are carefully investigated by Jeffreys who describes techniques to distinguish three components, CI, CII, and CIII, in the transient VEP response. He proposes that CI, which is partially sensitive to contrast, originates in the striate cortex (area 17), and that CII and CIII, which are mainly sensitive to contour, originate in different areas of the extra-striate cortex (areas 18 or 19 or both).

Kulikowski considers the correlation between visual contrast thresholds for grating stimuli evaluated psychophysically and by VEP measurement and discusses the relationship of grating-induced VEPs to pattern- and movement-sensitive mechanisms in the visual system. In another study involving grating stimuli, Bodis-Wollner and Hendley suggest that the response to counterphase grating modulation is determined by mechanisms which may be related to the transient- and sustained-type cells found in the visual system.

Regan describes some well-designed experiments in which steady-state pattern VEPs were obtained in response to changes in chromatic contrast rather than luminance contrast. By means of a feedback loop involving the stimulus and the VEP response, he was able to produce correlates of the field spectral sensitivities of the red- and green-sensitive colour mechanisms of the eye. The technique he used is an elegant VEP analogue of the psychophysical procedure employed by Stiles (1939, 1949) in his analysis of human colour vision. VEPs correlating in turn with overall photopic spectral sensitivity, with apparent motion effects and with depth changes in the stimulus are also described. Interestingly, May failed to obtain any VEP correlate of the contour-contingent chromatic after-effect known as the McCollough effect. He suggests that this may be a consequence of the effect being a steady-state phenomenon and thus not susceptible to investigatory procedures which depend on precise time-locking to the stimulus event.

The relationship between VEPs and eye movements is examined by several authors. Armington and Brooks each hypothesize that saccades produce VEPs because there is a rapid displacement of the retinal image, and Kurtzberg and Vaughan suggest that the existence of a VEP preceding the saccade might be associated with the mechanism responsible for programming the eye movement. VEP characteristics dependent upon the age of the subject are discussed by Harter, Crowell, Dustman, and their respective co-workers. The differences they observe in VEP properties in both infancy and in senescence are interpreted in terms of various mechanisms relating to neural organization.

Part 3 is concerned with clinical applications. It begins with the use of VEPs for essentially ophthalmological purposes. Arden and Sheorey describe a laser interference system for producing fringe-pattern stimuli, which, because of the low spatial frequencies they use, does not suffer from the disadvantages (speckle and poor quality high-frequency fringing) usually associated with laser-generated patterns. VEPs produced by reversal of the fringe patterns were shown to be reduced or absent in patients with opacities due to corneal or lenticular cataracts and vitreous hæmorrhage. A grating stimulus was also used by Maffei and his co-workers to investigate the visual function of subjects in which astigmatism is corrected optically. It was found that there is a residual asymmetry in VEP response with rotation of the stimulus which may be attributable to changes in the underlying neural function. The advantages of the objective nature of VEP methods in optometry are emphasized by Millodot, who points out, however, that except for newborn infants or uncommunicative patients, information from VEPs is no more useful than that obtained more easily and quickly by conventional methods. Sokol and Regan each describe experiments in which VEPs are used to assess visual function in patients with amblyopia.

There are several articles on the use of VEPs in the investigation of visual function in patients with multiple sclerosis or optic neuritis. By way of introduction, an excellent review of the known pathophysiology of conduction in central nerve fibres is given by McDonald. He suggests that although experiments on single demyelinated fibres show that VEP delays found in patients are explainable in terms of a simple reduction in conduction velocity, other factors, including a possible retinal effect, cannot be ruled out. Halliday, McDonald and Mushin in the next article discuss their clinical experiments with pattern-reversal transient VEPs. They demonstrated that there is a mean delay of 35 ms in the VEP response associated with the affected eye in unilateral optic neuritis and that a similar result holds in multiple sclerosis (*see also* Halliday, Halliday, Kriss, McDonald and Mushin, 1976). Analogous experiments were performed by Regan, Milner, and Heron using the complementary steady-state approach and Fourier analysis. Although medium-frequency flicker VEPs were found to be delayed in retrobulbar neuritis, high-frequency flicker VEPs were found not to be delayed. This, the authors hypothesize, may indicate that different neural processes within the visual pathway are preferentially damaged by the disease. (The reliability of this VEP method of assessment relative to psychophysical testing has been considered by Regan, Murray and Silver, 1977). Cook and Arden in their investigation of unilateral retrobulbar neuritis make the point that pattern-reversal VEP measurements imply conduction delays which are in magnitude about twice those obtained by other methods. They propose that one cause might be selective damage to Y-fibres, the X-fibres being left intact. (A careful investigation into pattern-reversal VEPs for the diagnosis of multiple sclerosis and optic neuritis has recently been published by Shahrokhi, Chiappa and Young, 1978. This study is based on the examination of two hundred patients.)

The book ends with a number of articles on the use of flash (unpatterned) stimulation in patients where the use of patterned stimuli is inappropriate. Harden and Pampligione discuss VEPs to flash in progressive neurometabolic 'storage' diseases of childhood and both Harding and Borda examine their usefulness in the evaluation of visual defects arising through, for example, lesions of the optic pathway. In contrast, Bodis-Wollner and his co-workers use grating stimuli in their study of VEPs from patients with cerebral lesions. They found that in some cases there is a dissociation of the detection of spatial contrast and local luminance which may relate to the division of response between sustained- and transient-type cells mentioned earlier.

In the introduction to this review, it was pointed out that there are certain difficulties associated with the VEP approach to the investigation of visual perception. Not least important of these is the question of the correlation between the VEP event and the selected stimulus attribute. It is essential that adequate control experiments are performed to ensure that the observed correlation is genuine and not the result of some concomitant peripheral nervous activity. It is also important, when there exists a significant intersubject variability, that this is taken into account in the interpretation of the experimental data. Not all contributors to the book deal with these issues entirely satisfactorily.

Despite its title, *Visual Evoked Potentials in Man: New Developments* contains material which has been available in the literature for several years. Nevertheless, it does contain previously unpublished work, and the fact that it brings together findings from a number of different sources and presents these in a reasonably unified and systematic fashion constitutes the principal attraction of the book. For someone wishing to apply VEP techniques to research into normal visual function or to clinical investigation, it provides a useful and comprehensive review of the field.

D. H. FOSTER

REFERENCES

ATTNEAVE, F. and MCREYNOLDS, P. (1950) A visual beat phenomenon. *American Journal of Psychology*, **60**, 107–110.

BURTON, G. J. (1973) Evidence for non-linear response processes in the human visual system from measurements on the thresholds of spatial beat frequencies. *Vision Research*, **13**, 1211–1225.

DONNER, K. O. and RUSHTON, W. A. H. (1959) Retinal stimulation by light substitution. *Journal of Physiology, London*, **149**, 288–302.

HALLIDAY, A. M., HALLIDAY, E., KRISS, A., MCDONALD, W. I. and MUSHIN, J. (1976) The pattern-evoked potential in compression of the anterior visual pathways. *Brain*, **99**, 357–374.

KAMP, A., SEM-JACOBSEN, C. W., STORM VAN LEEUWEN, W. and VAN DER TWEEL, L. H. (1960) Cortical responses to modulated light in the human subject. *Acta Physiologica Scandinavica*, **48**, 1–12.

REGAN, D. (1972) *Evoked Potentials in Psychology, Sensory Physiology and Clinical Medicine*. London: Chapman and Hall.

REGAN, D., MURRAY, T. J. and SILVER, R. (1977) Effect of body temperature on visual evoked potential delay and visual perception in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 1083-1091.

SHAHROKHI, F., CHIAPPA, K. H. and YOUNG, R. R. (1978) Pattern shift visual evoked responses. *Archives of Neurology, Chicago*, **35**, 65-71.

SPEKREIJSE, H. and OOSTING, H. (1970) Linearizing: A method for analysing and synthesizing nonlinear systems. *Kybernetik*, **7**, 22-31.

STILES, W. S. (1939) The directional sensitivity of the retina and the spectral sensitivities of the rods and cones. *Proceedings of the Royal Society, London*, **B127**, 64-105.

STILES, W. S. (1949) Increment thresholds and the mechanisms of colour vision. *Documenta Ophthalmologica*, **3**, 138-168.

Brain and Heart Infarct. Edited by K. J. Zulch, W. Kaufmann, K.-A. Hossmann and V. Hossmann. Berlin: Springer-Verlag. 1977. Pp. 349. Price DM 67.00.

This multi-author book is based on the proceedings of a symposium on cerebral and coronary vascular disorders held in Cologne, Federal Republic of Germany. There are 31 chapters that deal with the various metabolic, functional and pathological aspects of the normal and diseased heart and brain.

Coronary flow is influenced and regulated by both metabolic and extravascular factors of which oxygen consumption, heart rate and contractility are the most important. In the treatment of coronary vascular disorders drug research has focussed on Ca^{++} antagonists, whereas in cerebrovascular disease more attention has been paid to the actions of H^+ and K^+ ions. In the heart, therefore, Ca^{++} plays a decisive role though the interactions of the other ions play an important part in the adjustment of tissue demands for blood in the regulation of flow. There is an increasing body of evidence that a common denominator in the control of blood flow to the heart and brain is the nucleotide adenosine which is released from parenchymal tissue when the supply of oxygen becomes inadequate for the metabolic needs. Other factors, particularly H^+ and K^+ and possibly the myogenic mechanism, contribute to the regulation of myocardial and cerebral blood flow. The interrelationships between these various metabolic mediators remains uncertain. The regulation of the microcirculation in the heart is surprisingly similar to that of the brain, for example, an increase in $paCO_2$ may cause an increase in flow in some capillaries and a decrease in others. An outline of the regulation of brain energy metabolism under normoxic and hypoxic conditions is given.

The effects of ischæmia on the metabolism, blood flow and contractile state of the myocardium are discussed because of the implications for treatment. Studies have shown that discrete changes in metabolism occur in the brain in association with regional functional changes, and that these metabolic alterations are often linked to similar changes in local blood flow. Evidence is given in support of the theory of local metabolic control of regional cerebral blood flow. Recent work has shown that after 15-16 minutes of global cerebral ischæmia much of the neurological deficit sustained can be attributed to post-ischæmic changes which can be modified by treatment. The earlier in the post-ischæmic period the treatment is given, the better the expected recovery. However, after ischæmia of sufficient duration, application of any form of therapy will not improve recovery.

Studies of the coagulation system in patients with cerebrovascular disease have shown there is increased platelet aggregation in cases with transient ischæmic attacks (TIAs). Progressive ischæmia seemed to be related to decreased spontaneous fibrinolysis and hypercoagulability, while in completed stroke in the first three days fibrin degradation products were raised at a time when coagulation times were unchanged. Immediate thrombolytic therapy can be beneficial with progressive stroke. Following myocardial infarction signs of compensated coagulopathy and fibrin degradation products indicate intravascular coagulation. Fibrinolytic therapy leads to decrease in total peripheral resistance and tends to increase the cardiac output.

Complete cessation of cerebral blood flow causes an almost immediate suppression of higher CNS function followed by a breakdown of cell metabolism within a few minutes. There is new evidence that electrophysiological and biochemical functions during ischæmia have a certain capacity for recovery, even after normothermic cerebrocirculatory arrest of sixty minutes duration. Evidence is presented that the tolerance of the CNS to ischæmia does not depend on the ischæmic stress alone, but almost equally on post-ischæmic events. Work on myocardial ischæmia has shown that the heart is able to sustain normal work when there is a reduced amount of ATP. The study of neurological deficits and neuronal function in experimental models of acute focal cerebral ischæmia has contributed towards the rational assessment of effective therapeutic measures. Similar work with experimental heart infarction has shown there is an increased vascular capacity in the subendocardial tissue, that subendocardial perfusion is sensitive to augmented load and that restriction of subendocardial blood supply is most pronounced under conditions when local perfusion pressure is diminished by a compromised vasculature, for instance by atheroma.

An elegant description of cerebral blood flow measured by multidetectors and isotope techniques in the production of cerebral 'ideograms' and functional 'landscapes' is given. It has been shown that even though mean hemispheric flow may only change to a limited extent, important regional alterations take place, often amounting to 50 per cent or more during physiological changes which accompany sensorimotor and mental activity. Such changes lead to a redistribution of flow from inactive to active regions. This takes place by means of inherent tissue mechanisms which are responsible for the metabolic regulation of cerebral blood flow.

Chronic hypertension is the most common cause of heart failure, the mechanism being an increase in intraventricular pressure and demand for oxygen by the myocardium, hypoxia and ultimate impairment of the contractibility of the left ventricle. In chronic arterial hypertension the absolute value of cerebral blood flow is the same as in normotension. However, autoregulation of cerebral blood flow adapts in such a way the lower and upper limits of autoregulation are shifted towards higher values on the blood pressure axis. Recent work suggests that acute hypertensive encephalopathy is caused by overstretching of the arteriolar walls, this leading to extravasation of plasma proteins and the formation of focal cerebral œdema. Studies have also shown that the lower limit of autoregulation is shifted upwards in cases with extracranial vascular disease. Evidence is presented that suggests focal symptoms related to a reduction in blood pressure are rare and are probably due to micro-embolism rather than hæmodynamic consequences of loss of autoregulation with declining blood pressure.

The presence or absence of cardiac embolism and hypertension have been assessed in a group of patients with cerebral infarction. It was found that idiopathic atrial fibrillation appeared to play a major role in cerebral embolism. Major advances are reported in the understanding of the factors influencing the progression and the regression of the advanced atheromatous plaque in coronary arteries. The relationship between advanced atheroma and myocardial ischæmia is considered. It seems that atheroma is an almost entirely preventable and substantially reversible disease process, and that many of its clinical effects may be counteracted by prompt and skilful treatment.

Comparison of the characteristics of subjects developing myocardial infarction with those with atherothrombotic brain infarction shows both similarities and differences, for example, age, sex, hypertension, serum cholesterol, cigarette smoking, diabetes and polycythæmia. A model of TIAs by arachidonic acid-induced platelet emboli and the protective effect of pretreatment with aspirin is described. Transient ischæmic events of the heart are generally ascribed to fixed atherosclerotic obstructive coronary disease, though other possibilities are considered. It used to be thought that TIAs were due to general hæmodynamic factors whereas emphasis is now placed on the role played by the various mechanisms involved in thrombogenesis and hæmostasis. Indeed there is recent evidence that aspirin conclusively reduces the number of both TIAs and cerebral infarcts in patients with carotid territory TIAs. The traditional view is that ischæmic heart disease is due to thrombotic occlusion of coronary arteries, but there is substantial evidence that acute thrombus formation does not precipitate acute fatal ischæmic heart disease but rather that coronary thrombus is a consequence rather than a precipitating cause of acute myocardial infarction. The proper management of patients with cerebral ischæmia and infarction depends on its ætiology, its state of evolution and the relationship between the disease and the general condition of the patient. There is an emerging emphasis on the management of TIAs by admission to hospital, anticoagulants, angiography and surgical treatment if indicated. The therapy of myocardial infarction and coronary heart disease is dictated by the prevention of angina pectoris, the intermediate syndrome and myocardial infarction.

This is probably the first symposium at which joint discussions on the circulatory disorders of the brain and heart, two of the most common diseases in clinical practice, have taken place. Particular emphasis has been placed on the differences and similarities of the control of cerebral and myocardial blood flow and the pathophysiology of brain and heart infarction. The authors have therefore discussed the various facets of the central question, and in so doing have produced a series of well written, liberally illustrated and informative chapters. Appended to each is a useful bibliography and a subject index is provided at the end of the proceedings. This book will be of considerable value to anyone with either an interest in, or who is working in, the fields of cerebral and myocardial ischæmia.

D. I. GRAHAM

Handbook of Clinical Neurology. Vol. 30. Congenital Malformations of the Brain and Skull. Edited by P. J. Vinken and G. W. Bruyn with N. C. Myrianthopoulos. 1977. Amsterdam: North-Holland Publishing Company. Price Dfl. 280.00.

This volume opens with 5 general chapters on classification, developmental anatomy, errors in differentiation of the central nervous system and ætiology and epidemiology. These are authoritative and of particular value to the pædiatric neurologist. The remaining 22 chapters deal with a wide range of congenital and developmental anomalies, some very rare and others relatively common. Ettlinger provides a useful review of agenesis of the corpus callosum and Larroche gives a good account of cytoarchitectonic abnormalities. De Lange (progressive hydrocephalus and treatment of hydrocephalus), Salam (stenosis of the aquaduct of Silvius) and Joe R. Brown (the Dandy-Walker syndrome) are among others who excel. Robinson gives a detailed account of agenesis and anomalies of other brain structures.

This is a book of reference and as such will be required in departmental libraries.

R. A. HENSON

Reflex Epilepsy, Behavioral Therapy and Conditional Reflexes. By Francis M. Forster. 1977. Pp. 318. Springfield, Illinois: C. C. Thomas. Price $22.75.

The term reflex epilepsy is probably more familiar to older than to younger neurologists. Nowadays we tend to speak of evoked epilepsy, a name which carries no particular implications on causation. Although rare, evoked epilepsy has exercised the interest of neurologists for many years. Evoking sensory factors are present in some 5 to 6 per cent of epileptic patients. Dr. Forster is well-known for his work in the field, and this volume represents the distillation of his wide experience.

From 1961 onwards Dr. Forster investigated 73 patients with reflex epilepsy. In 39 the seizures were visually induced, while 10 were sonogenic and 5 musicogenic; 11 were linked with reading and other uses of language. His account of his clinical findings and detailed EEG studies occupies the major part of the book, and neurologists will welcome this concentration of information on a series of strange and sometimes rare phenomena within one volume. The later chapters deal with behavioural methods of treatment which were particularly successful in musicogenic epilepsy, though gratifying results were also obtained in visually-induced and reading epilepsy. Dr. Forster concludes that, on balance, reflex epilepsy is not based on a conditional (sic) reflex.

This book is not easy to read despite its interest. Dr. Forster has an occasional tendency to idiosyncratic verbal usage which causes difficulty in understanding. Nevertheless, his book is recommended for its unique contents. The price is reasonable.

R. A. HENSON

A Colour Atlas of Neuropathology. By C. S. Treip. 1978. Pp. 208. London. Wolfe Medical Publications Limited. Price £15.00.

This is more than an atlas yet not quite a textbook. In addition to over 300 illustrations—the great majority of the photomicrographs being in colour—it incorporates a concise yet lucid account of the major aspects of neuropathology, a brief appendix incorporating some useful technical information, and a bibliography. Designed as an introductory manual of neuropathology it should be of considerable value to pathologists in training, and clinicians in training in any branch of the neurosciences could hardly fail to benefit from browsing in it. It also seems good value for money.

Despite its undoubted assets the atlas does have some deficiencies. I refer in particular to some of the colour illustrations, albeit small in number, which are most unlike what I would expect to see under a microscope. Indeed one or two are frankly misleading. Thus, differentiating between non-specific or autolytic changes in neurons and the specific cytological changes of recent necrosis and infarction is one of the most difficult problems encountered by the trainee pathologist: he will find little help from Figs. 2, 5, 6 and 99. The black and white illustrations on the other hand are superb, and one again wonders how important coloured illustrations are in an atlas of pathology except when a particular staining reaction has to be shown

I am sure however that Dr. Treip will have the chance to remedy the few pictorial defects since I feel sure that there will be a demand for a second edition. I would also suggest that the pathology of raised intracranial pressure is too important to be restricted to three pages in the chapter on Vascular Disease, and that it might be a good idea to emphasise the near impossibility of recognising recent hypoxic brain damage, even when it is severe and extensive, without an informed histological study, rather than simply illustrating the relatively rare cases where there are obvious macroscopic abnormalities in the brain.

HUME ADAMS

Pain in the Trigeminal Region. Edited by D. J. Anderson and B. Matthews. 1977. Pp. 453. Amsterdam and New York: Elsevier/North Holland Biomedical Press. Price: $49.50; Dfl. 121.00.

Pain in the Trigeminal Region is a collection of papers delivered by many investigators at a symposium held at Bristol University. As the symposium was organized by a department of research in oral biology, the trigeminal region is very much the trigeminal region related to teeth; and most of the work reported was done on cats and rabbits. The work is of the highest standard; both as consumers of dental treatment, and as neurologists, we will find nearly all the papers of great interest.

One of the papers unrelated to teeth was a study of Beuerman, Maurice and Tanelian of thermal sensibility in the human cornea. With a clever and original technique, they were able to conclude that the cornea possesses no thermal sensibility. Saline at temperatures over 40–43° C. did not feel warm but caused a sensation of pain, often of burning pain.

There are several important anatomical studies. Kruger has continued his study of the fifth nerve, in the cat, and its connections, now using modern methods based on axonal protein transport. He and his colleagues conclude that the principal nucleus is homologous with posterior column nuclei, nucleus interpolaris is in part homologous with the lateral cuneate nucleus, and the nucleus caudalis with the substantia gelatinosa of the posterior horn. An important contribution is that of Gobel, Falls and Hockfield. They divide, in the cat, the grey matter of the region extending from the obex to the spinal cord into eight laminæ, corresponding to those of Rexed for the first eight laminæ of the spinal cord. Many of the contributors report their studies of neurons of the nuclei caudalis and oralis of the trigeminal nerve and of the neighbouring reticular formation, which receive noxious and thermal input. It was reported that the activity of neurons receiving noxious input from tooth pulp and from the skin of the cat could be inhibited by immediately previous tactile stimulation of the forepaw, excitation of the superior laryngeal nerve, infra-orbital nerve, the opposite somatosensory cortex and, above all, by stimulation of the periaqueductal grey matter. Stimulation of the latter neurons inhibited the activity of all neurons of nuclei oralis and caudalis. The effect of this stimulation could be reversed by naloxone.

There are two papers on inhibition of these nociceptive neurons by excitation of brain-stem raphe nuclei. Lovick, West and Wolstencroft stimulated the raphe nuclei and also activated these neurons antidromically. They calculated the conduction rate of the raphe-trigeminal fibrès as 6·5–1·5 m/s.

Andersen, Lund and Puil reported that morphine was fixed on neurons of nucleus caudalis and stopped their ongoing or spontaneous firing. Enkephalin had the same effect and prevented the neurons being fired by stimulation of tooth pulp. Both these actions were reversed by naloxone. These investigators and Henry, Hu, Lucier and Sessle also showed that substance P activated and increased the after-discharge of neurons receiving a noxious input and had no effect on those receiving an input from tactile and mechano-receptors. Thus, as is now being found generally, the action of substance P is the opposite of that of enkephalin and morphine. In peripheral tissues, substance P is always found near blood vessels. Curiously, the anatomy and physiology of co-ordination of stimulation of the face with movements of the neck to remove the face and head from the stimulus has been inadequately investigated. This subject was reported upon in an unusual communication by Abrahams and Richmond.

This was a valuable symposium. It is an achievement to have the book ready for sale five months after it was held. Printed on the cover of the book there is an appropriate stone carving on a capital in Wells Cathedral. It is regrettable that the price is so high.

P. W. NATHAN

Essays in Neurochemistry & Neuropathology. Vol. 2. Edited by M. B. H. Youdim, W. Loveenberg, D. F. Sharman and J. R. Lagnado. 1977. Pp. 174. Chichester, New York: John Wiley. Price £8.75; $17.50.

This book is a useful account of the current status of the rapidly developing subject of neuropharmacology. There are six essays in this second volume under review, several of which deal with controversial topics related to the biochemical basis of mental illness. Such questions as the mode of action of hallucinogens and their relevance to schizophrenia and the relationship between synaptic activity and behaviour are critically discussed. There is also a chapter on cyclic nucleotides and postsynaptic transmission which clearly relates to the mechanism of action of neuroleptics. Another topical essay deals with prospective neurotransmitters in the retina and their cellular localization. Equally absorbing is a rather more practical discussion of the value of the isolated rat brain preparation for assessing metabolic processes and electrical activity of the CNS.

For an ephemeral publication the book is well produced and reasonably priced. It can be commended to the general reader as well as those interested in psychopharmacology.

A. N. DAVISON

Immunosuppressive Treatment in Multiple Sclerosis. Edited by P. Delmotte, O. R. Hommes and R. Gonsette. 1977. Pp. 224. Ghent: European Press. Price not stated.

The search for the therapeutic philosopher's stone in multiple sclerosis continues and the way is made little clearer by this publication. The introduction states that immunosuppressive therapy is the best treatment we have in multiple sclerosis, but the conclusion that it alters the course of the disease is at best tentative.

The pattern of the book is a series of papers followed by a brief discussion It begins with an unimpressive chapter on immunological abnormalities in multiple sclerosis and experimental allergic encephalomyelitis and compares them, followed by a brief review of immunosuppressive agents. The first chapter on therapeutic trials refers to the use of azathioprine in relapsing multiple sclerosis and is a retrospective study in which some patients were treated As is customary in such work the apparent efficacy of the treatment derives more from a deterioration in the controls than benefit to the treated patients. This is followed by a chapter on the chronic progressive form of multiple sclerosis and concerns the use of cyclophosphamide. Again this study is uncontrolled and contains some surprising statistical techniques to obtain the apparent benefit of the treatment to the patient. There are additional chapters on long-term immunosuppression with various drugs (using a dubious technique of comparing the pretreatment relapse rate as a control), and short-term intensive immunosuppression concluding that relapses when they occur are less severe (a difficult criterion). The Munich group give further details on thoracic duct drainage and Cendrowski reports his negative work with Levamisole. In addition to this there are chapters on CSF IgG during immunosuppression and pathology of multiple sclerosis.

In all work with multiple sclerosis there is a desperate need for strict controls and yet this book has only two chapters on a double-blind immunosuppressant trial, which is at such an early stage that no data on its effect are available. Indeed in the concluding discussion some of the participants state that controlled trials betray the trust of the patient. However, if any real advance is to be made such trials have to be conducted. It is a pity that many of the papers in this book contain evidence that immunosuppression might be of value in multiple sclerosis, yet none prove this, solely because there are no adequate trials.

PETER RUDGE

Brain

General Index

A re-issue of the first part of the General Index, covering Volumes 1–23 (1878–1900) and a recently compiled second part covering Volumes 24–48 (1901–1925) are now available to subscribers at £2·00 each, postage Part 1 (25p) Part 2 (20p) Parts 1 and 2 (40p). A third part (1926–1950) will follow.

Please write, enclosing money with order, to:
Wm. Dawson and Sons Ltd.,
Back Issues Department,
Cannon House,
Folkestone, Kent CT19 5EE, England.

Back issues of BRAIN can also be obtained from Wm. Dawson and Sons Limited. Please apply direct for prices and availability.

CHARLES C THOMAS • PUBLISHER

PATHOLOGY IN COMPUTED TOMOGRAPHY OF THE BRAIN *by* **Scott D. Henderson,** *Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.* The large number of scans included in this volume will familiarize the reader with pathology as demonstrated on such scans. Analyses are presented in general terms. The author stresses the correlation of clinical data and other diagnostic procedures to arrive at a correct diagnosis. *'78, 216 pp. (6 3/8 x 9 5/8), 839 il., $17.50*

HOW TO EXAMINE THE NERVOUS SYSTEM: Techniques and Methods *by* **R. T. Ross,** *Univ. of Manitoba, Winnipeg, Manitoba, Canada.* Presented in a uniquely appropriate format, this book will provide the student with the skills needed for nervous system examinations. Individual chapters cover such areas as the fundus oculi, eye movement, cranial nerve involvement, reflexes, sensation, the corticospinal tract syndrome, and cerebellar signs. *'78, 136 pp. (4 1/2 x 7), 44 il., $6.50, Lexide*

AN ATLAS OF POLYTOME PNEUMOGRAPHY: With Particular Reference to the Midline Ventricles of the Brain *by* **Taher El Gammal** *and* **Marshall B. Allen, Jr.,** *both of Medical College of Georgia, Augusta, Georgia. Assisted by* **Paul Dyken.** This atlas presents a large number of studies which supplement the study of normal anatomy of the cerebrospinal fluid pathways, and provides comparisons for the identification of abnormal structures. *'77, 480 pp. (8 1/2 x 11), 729 il., $39.50*

SPEECH THERAPY AND THE BOBATH APPROACH TO CEREBRAL PALSY (5th Ptg.) *by* **Marie C. Crickmay,** *Gorge Road Hospital, Victoria, British Columbia, Canada.* This is an ideal text for those who want to know more about the Bobath approach to cerebral palsy. The author concentrates on the neurophysiological principles which form the basis of this method, and demonstrates their application. Also described are principles of speech pathology; articulation, language and fluency problems; and psychological aspects. *'77, 192 pp., 19 il., $10.00*

CEREBRAL LOGIC: Solving the Problem of Mind and Brain *by* **Charles W. Needham,** *Neurological Associates of Tucson, Tucson, Arizona.* In its inquiry into the neurophysiology of consciousness, this book considers equally the disciplines of neurology, philosophy, and psychology. A discussion of the general nature of the mind-brain problem is followed by a look at the origin of mentalistic language and its applicability to cerebral logic. *'78, 232 pp., 1 il., $12.75*

MEDICAL ASPECTS OF MENTAL RETARDATION (2nd Ed.) *edited by* **Charles H. Carter,** *Sunland Center, Orlando, Florida. (33 Contributors)* This completely revamped Second Edition examines genetics and cytogenetics, infections, trauma, cranial abnormalities, poisons, nutrition, and prenatal and postnatal damage. Community diagnostic and treatment centers, cerebral pathology and metabolism, and treatment with drugs are also explored. *'78, 912 pp. (6 3/4 x 9 3/4), 436 il., 47 tables, $59.50*

LEUKEMIA AND LYMPHOMA IN THE NERVOUS SYSTEM *edited by* **Carl Pochedly,** *Nassau County Medical Center, East Meadow, New York. Foreword by* **Alvin M. Mauer.** *(3 Contributors)* The author reviews clinical manifestations of leukemia and lymphoma as they affect the nervous system, the mechanisms that give rise to these manifestations; and the rationale and techniques for prevention and treatment. He includes data on histopathology, cytological methods for CSF examination, and neurological complications. *'77, 248 pp., 42 il., 26 tables, $23.50*

GRINKER'S NEUROLOGY (7th Ed.) *by* **Nicholas A. Vick,** *Northwestern Univ. School of Medicine, Evanston, Illinois.* In its review of this Seventh Edition, the *Journal of Neurosurgery* said, "This new edition . . . will be of great value to practicing neurosurgeons and neurologists. There is concise coverage of almost every conceivable neurological syndrome and a greatly expanded, up-to-date bibliography. Hence, it is an important reference book for the busy clinician." *'76, 1104 pp. (6 3/8 x 9 5/8), 472 il., 29 tables, $43.50*

Orders with remittance sent by air, postpaid

301-327 East Lawrence Avenue • Springfield • Illinois • 62717 • USA

PRINTED IN GREAT BRITAIN AT THE UNIVERSITY PRESS, OXFORD
BY VIVIAN RIDLER, PRINTER TO THE UNIVERSITY

Rec.
26.6.79

ISSN 0006-8950

Brain

A Journal of Neurology

Volume 101 Part IV December 1978

Hemisphere Function and Binocular Depth Perception. G. Danta, R. C. Hilton and D. J. O'Boyle 569

A Clinical and Genetic Study of Spinal Muscular Atrophy of Adult Onset. John H. Pearn, Peter Hudgson and John N. Walton 591

The Role of Frontal and Parietal Cortex in Cognitive Processing. Betty Ann Brody and Karl H. Pribram 607

Long Latency Event-related Components of the Auditory Evoked Potential in Dementia. Douglas S. Goodin, Kenneth C. Squires and Arnold Starr .. 635

Selective Blockade by Scopolamine of Synaptic Responses in Cat's Caudate Nucleus and its Modification by Lesions of the Substantia Nigra. R. Spehlmann, K. Norcross and E. J. Grimmer 649

Measurements of Visual Evoked Potentials in Parkinson's Disease. Ivan Bodis-Wollner and Melvin D. Yahr 661

The Concept of a Sensorimotor Cortex: Its Early History, with Especial Emphasis on Two Early Experimental Contributions by W. Bechterew. Alfred Meyer 673

Epileptic Brain Damage: The Role of Systemic Factors that Modify Cerebral Energy Metabolism. G. Blennow, J. B. Brierley, B. S. Meldrum and B. K. Siesjö 687

Effect of Ethanol on Neuronal Activity in the Parietal Association Cortex of Alert Monkeys. J. Hyvärinen, M. Laakso, R. Roine, L. Leinonen and H. Sippel 701

Notices of Recent Publications 717

Index 724

OXFORD: AT THE CLARENDON PRESS

Edited by C. G. PHILLIPS
Deputy Editor R. A. HENSON
with the help of

J. HUME ADAMS	R. W. GILLIATT	M. VOGT
A. N. DAVISON	E. C. HUTCHINSON	L. WEISKRANTZ

Assistant Editor E. MACDOUGALL
Secretary and Treasurer J. M. NEWSOM DAVIS

All editorial correspondence, typescripts and books for review to be addressed to The Editor of *Brain*, Hertford College, Oxford, OX1 3BW

Directions to Authors upon the Preparation of Papers

PAPERS must be typewritten on one side of the paper only and double-spaced, and submitted in duplicate with two sets of figures In addition to the full title of the paper, authors should supply a 'running title' which will appear at the heads of the pages *Brain* does not publish preliminary reports of work in progress: only exceptionally does it publish detailed studies of a single case Papers reporting experiments on patients or healthy volunteers must record the fact that the subjects' informed consent was obtained (Declaration of Helsinki: *Brit. Med. J* 1964, 2, 177). The typescript should be carefully and finally revised before submission to the Editor, so that if the paper is accepted it is ready for the printer Clarity of style and brevity of expression are essential. Before submitting a paper it is always valuable to obtain the comments of colleagues who are unfamiliar with the work. We refer intending authors to the *Journal of Physiology*'s 'Suggestions to Authors' price 10p post-free from Cambridge University Press, Box 92, 200 Euston Road, London, NW1

The paper should be accompanied by a declaration in the following terms 'The work reported in the attached paper entitled . . . has not been, and is not intended to be, published anywhere except in *Brain*.'

BIBLIOGRAPHIC REFERENCES should be limited to essential literature; they should be listed at the end of the paper in alphabetical order, and not numbered. *In the case of a Journal*: author's name, date of publication in brackets, are followed by the title of the paper, the name of the Journal *in full* and underlined for italics, the volume number and the first and last page numbers of the paper quoted, both in Arabic numerals. *In the case of a book*: author's name, date of publication in brackets, title of book underlined for italics, place of publication, publisher's name, chapter and page numbers in Arabic numerals Works by the same author should be given in chronological order, and if there be more than one in a year, they are marked *a*, *b*, *c*, etc.; when an author's name recurs a short line is used. *In the text* numbered references are not used, but the author's name is followed by the appropriate year in brackets.

ILLUSTRATIONS should, where possible, be line drawings in Indian ink on separate white boards, numbered, and with the author's name on the back. Drawings and other illustrations should not exceed twice the size of the reproduction and thus lines must be thick enough to show up after reduction. This applies also to the lettering and numbering which the authors are asked to provide. Legends should be on separate sheets and numbered. Desired positions of tables and figures should be marked by writing instructions enclosed within lines and brackets, e g. (*Table 3 near here*) or (*Fig. 4 near here*).

Half-tone photographs must be kept to a minimum. Excellent photographs with clear contrast are essential, especially for the reproduction of electron micrographs. Authors may be asked to contribute to their cost There should be a bar on all micrographs giving magnification, e.g. 1 μm.

Authors are asked not to reprint their papers, or to authorize others to do so, without first consulting the Oxford University Press (Academic Division), Walton Street, Oxford, OX2 6DP.

Fifty free offprints are sent to the authors, who may order more direct from Oxford University Press, Walton Street, Oxford, OX2 6DP when they get their proofs.

Subscription rate for an annual volume of four issues: £19.00 ($42) post free, or for subscribers resident in the U.K £16 50. Single Issue: £5.00 ($12) net, postage extra.

Please address correspondence on business matters as follows·

Subscriptions to the current volume. Subscriptions Department, Oxford University Press, Press Road, Neasden, London, NW10 0DD.

Orders and inquiries for back numbers: Wm. Dawson & Sons Limited, Cannon House, Folkestone, Kent.

Inquiries about advertising, offprints and copyright: Academic Division, Oxford University Press, Walton Street, Oxford, OX2 6DP

Brain

A Journal of Neurology

Volume 101 Part IV December 1978

Hemisphere Function and Binocular Depth Perception. G. Danta, R. C. Hilton and D. J. O'Boyle 569

A Clinical and Genetic Study of Spinal Muscular Atrophy of Adult Onset. John H. Pearn, Peter Hudgson and John N. Walton 591

The Role of Frontal and Parietal Cortex in Cognitive Processing. Betty Ann Brody and Karl H. Pribram 607

Long Latency Event-related Components of the Auditory Evoked Potential in Dementia. Douglas S. Goodin, Kenneth C. Squires and Arnold Starr .. 635

Selective Blockade by Scopolamine of Synaptic Responses in Cat's Caudate Nucleus and its Modification by Lesions of the Substantia Nigra. R. Spehlmann, K. Norcross and E. J. Grimmer 649

Measurements of Visual Evoked Potentials in Parkinson's Disease. Ivan Bodis-Wollner and Melvin D. Yahr 661

The Concept of a Sensorimotor Cortex: Its Early History, with Especial Emphasis on Two Early Experimental Contributions by W. Bechterew. Alfred Meyer 673

Epileptic Brain Damage: The Role of Systemic Factors that Modify Cerebral Energy Metabolism. G. Blennow, J. B. Brierley, B. S. Meldrum and B. K. Siesjö 687

Effect of Ethanol on Neuronal Activity in the Parietal Association Cortex of Alert Monkeys. J. Hyvärinen, M. Laakso, R. Roine, L. Leinonen and H. Sippel 701

Notices of Recent Publications 717

Index 724

Brain Research Reviews

ANNOUNCING

a volume of Brain Research devoted to the publication of high quality review articles.

Editor-in-chief: D.P Purpura, Bronx, N.Y

The recent remarkable growth of neuroscience research and the progressively increasing problem of assimilating new data have greatly enhanced the value of well-organized, topical Review Articles. At the same time, pressures for publication space in Brain Research for original Research Reports and Short Communications have limited the number of meritonous Review Articles that can be accommodated annually. To avoid future competition for available space a supplementary volume entitled, Brain Research Reviews, will be published beginning in early 1979 and thereafter It is expected that this volume will be devoted to Review Articles and occasionally long research papers with extensive review components and that it will meet the demands for rapid publication of analytical surveys that define heuristic hypothesis and provide new insights into brain mechanisms.

Brain Research Reviews will commence publication in the first quarter of 1979 and will be produced within the same editorial and production framework as Brain Research itself. It will form an integral part of the subscription to Brain Research, but will also be available separately to non-subscribers.

Brain Research Reviews
1979 Volume 180/BRR Volume I
Subscription Price: US $ 66.75/Dfl 150 00 including postage.

Brain Research,
1979 Volumes 159-180
Subscription Price: US $ 1446.75/Dfl 3300.00

ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS

send your orders or requests for free specimen copies

In the U.S.A. and Canada:
JOURNAL INFORMATION CENTER
Elsevier's Science Division
52 Vanderbilt Ave ,
New York, NY 10017

In all other countries:
ELSEVIER/NORTH-HOLLAND
BIOMEDICAL PRESS
P.O. Box 211, Amsterdam,
The Netherlands

The Dutch guilder price is definitive. US $ prices are subject to exchange rate fluctuations

THE BRITISH JOURNAL OF PSYCHOLOGY

The British Journal of Psychology is published by Cambridge University Press for the British Psychological Society. It deals with general and experimental psychology, publishing papers which are not suitable for the Society's more specialised journals.

It also contains a large book review section which covers publications in German as well as English

Contents of Volume 69 Part 2 May 1978

MICHAEL W EYSENCK Levels of Processing: A Critique
ROBERT S LOCKHART and FERGUS I.M CRAIK Levels of Processing: A Reply to Eysenck
MICHAEL W. EYSENCK. Levels of Processing: A reply to Lockhart and Craik
W.R. CROZIER. Evaluating The Worth of Gambles
STUART J. McKELVIE. Graphic Rating Scales- How Many Categories
B.S. GUPTA and MOHANJEET NAGPAL. Impulsivity/sociability and reinforcement in verbal operant conditioning
STANLEY COREN and CLARE PORAC: The Validity and reliability of self- report items for the measurement of lateral preference
J.M. VON WRIGHT, P. LOIKKANEN and P REIJONEN. A Note on the Development of Recall in Spatial Location
J B DEREGOWSKI: Role of Symmetry in Pattern Reproduction
PETER WALKER and R.R. MEYER The Subliminal Perception of Movement and the course of autokinesis
A AHLUWALIA· An Intra-Cultural investigation of suseptability to 'Perspective' and 'Non-perspective' spatial illusions
I.M CORNISH· Memory for Prose: Quantitative analysis of Recall Components
RONALD F. JARMAN· Level 1 and Level 11 Abilities: Some Theoretical Reinterpretations
L. HARTLEY, T. HENRY and J:COOPER–SMARTT. Chlorpromazine and Serial Reaction Performance
Book Reviews

Volume 69 (1978) **£23.00** ($52.00 U.S.A. & Canada)
Single Parts £7.00 ($15.50 U.S.A. & Canada) **each**

CAMBRIDGE UNIVERSITY PRESS
Bentley House, 200 Euston Road, London NW1 2DB
32 East 57th Street, New York, N.Y. 10022

TWO IMPORTANT BOOKS FROM CHURCHILL LIVINGSTONE

NEW EDITION To be published soon

Nerves and Nerve Injuries *Sir Sydney Sunderland*

1978 Second edition 1,072 pages approx illustrated £55.00

A comprehensive review of the entire subject—the only reference text at this level—new edition largely rewritten, revised and updated

NEW VOLUME

Recent Advances in Clinical Neurology—2 Edited by *W. B. Matthews* and *Gilbert H. Glaser*

224 pages illustrated hardback £10.00

Recent advances in this field are covered by ten internationally acclaimed experts, giving up-to-date accounts of a variety of topics in clinical neurology, neurophysiology, neurosurgery and neuroradiology

Churchill Livingstone, 23 Ravelston Terrace, Edinburgh EH4 3TL

New Books from Blackwell

Clinical Neuroimmunology

Edited by F. Clifford Rose. December 1978. 544 pages, 70 illustrations. £25.00

The steady development in the application of immunology to neurological disorders has accelerated in recent years resulting in exciting advances in knowledge and dramatic improvements in both diagnosis and treatment. This volume reviews the present state of our understanding and provides substantial evidence that we are on the verge of even greater discoveries.

Contents: General aspects; Muscle disease; Peripheral neuropathies; Motor neurone disease; Multiple sclerosis. Virology; Malignancy; Therapy.

Some other titles of related interest

Relief of Pain in Clinical Practice

S. Lipton. Early 1979. 464 pages, 93 illustrations. About £20.00

This up-to-date manual deals with the more important and common intractable painful conditions and the most effective methods of dealing with them.

Therapeutics in Neurology

D.B. Calne. Second Edition, Spring 1979. 640 pages, 160 illustrations. About £22.50

In this second edition the author has completely revised the text and has introduced seven new chapters covering growing areas of research and practical pharmacotherapy.

Blackwell Scientific Publications

JOURNAL OF MENTAL DEFICIENCY RESEARCH

Editor: Dr B. W. Richards

THE JOURNAL OF MENTAL DEFICIENCY RESEARCH contains original research on medical and psychological problems relevant to mental sub normality.

Recent articles include:

The Recurrence of Mongolism in Sibships, B. W. Richards

Serum Cholinesterase (Pseudocholinesterase) in Down's Syndrome: 1. Phenotype Frequencies at the E_1 and E_2 Loci, Anne H. Drew and A. T. Rundle

The Use of the Vineland Social Maturity Scale, the Merrill-Palmer Scale of Mental Tests (Non-Verbal Items) and the Reynell Developmental Language Scales with Children in Contact with the Services for Severe Mental Retardation, Judith Gould

Chemical Analysis of an Angiofibroma from a Patient with Tuberous Sclerosis, M. H. Fischer, J. S. Fortune, S. H. Foster and B. H. Gilbert

The Ante-Natal Detection of Down's Syndrome: Some Demographic Aspects, D. P. Forster

Double Autosomal Trisomy: (48,XX,+18,+21): Case Report and Review of Literature, K.-P. Grosse and G. Schwantitz. **Appendix: Results of Dermatoglyphic Analysis,** Danuta Loesch

Interchromosomal Duplication for the Short Arm of Chromosome No. 9: Report of Three Cases Due to a Familial Translocation t(9;11) and One Case with a De Novo 47,XX,+9p Karyotype, C. C. Lin, G. Holman, L. Sewell, P. Bowen and B. Bierderman. **Appendix: Results of Dermatoglyphic Analysis,** Danuta Loesch

Published quarterly by
THE NATIONAL SOCIETY FOR MENTALLY HANDICAPPED CHILDREN
Pembridge Hall, 17 Pembridge Square, London W2 4EP

Yearly Subscription £10.00 U.S.A. $30.00

Gerhard D. Wassermann: NEUROBIOLOGICAL THEORY OF PSYCHOLOGICAL PHENOMENA
Wassermann takes a refreshingly original look at the way in which the human nervous system could generate and represent both perceptual and cognitive phenomena as well as actions. He uses his theory to explain a considerable variety of phenomena, including a possible neural basis of memory, depth perception, aspects of Gestalt psychology, and possible representations of concepts and language. It is both controversial and stimulating – a must for all those interested in the relations between brain, behaviour and developmental biology.
1978, £15.00, 0 333 23792 7

For further information please contact:
Rosemary David(B), Macmillan Press Ltd, 4 Little Essex St., London WC2R 3LF

MACMILLAN PRESS

Developmental Dysphasia

edited by Maria A. Wyke
October/November 1978, xii + 180pp., £7.80/$ 16.15 0.12.766950.7

Developmental dysphasia, the deficit in the acquisition of normal language functions in children of normal or above intelligence and with adequate hearing ability to permit the perception of verbal sounds, has attracted considerable attention for a number of years. The problem has engaged the interest of scientists from very different fields, and many attempts have been made to unravel the essential nature of the disability. For a long time the deficits of children with developmental dysphasia had been merely observed and recorded, but lately there has been an increased number of investigations which have viewed developmental dysphasia in the light of more rigorous experimental procedures. This book presents an up-to-date account of work carried out in the field of developmental dysphasia. The approach is mult-disciplinary and the volume assembles contributions from neurologists, psychologists, linguists, speech therapists and remedial teachers, all of whom have had close contact with the problem.

Academic Press
London New York San Francisco
A Subsidiary of Harcourt Brace Jovanovich, Publishers
24-28 Oval Road, London NW1, England
111 Fifth Avenue, New York, NY 10003, USA

NEW

the first comprehensive methodology journal in this field

CALL FOR PAPERS

JOURNAL OF NEUROSCIENCE METHODS

editor-in-chief
J.S. KELLY
MRC Neurochemical Pharmacology Unit, Department of Pharmacology, Medical School, Hills Road, Cambridge CB2 2QD, U K

associate editors
V.E. DIONNE, Burlington, VT, U S A **E.G. MERRILL,** London, U K **F. VANDESANDE,** Ghent, Belgium

aims and scope
The **Journal of Neuroscience Methods** will publish research papers and a limited number of broad and critical reviews dealing with new methods or significant developments of recognised methods, used to investigate the organisation and fine structure, biochemistry, histo- and cyto-chemistry, physiology, biophysics, and pharmacology of receptors, neurones, synapses and glial cells in the nervous system of man, vertebrates and invertebrates These studies may also be applicable to the clinical and behavioural sciences, tissue culture, neurocommunications, biocybernetics or computer software
Although articles should be written in sufficient detail to allow others to verify these methods, they should also be intelligible to a broad scientific audience In addition, the journal will publish letters sent in camera-ready format, on paper supplied by the editorial office, containing comments or discussion of methodology described in this journal or any other journal devoted to the neurosciences

editorial board
S. Andersson, Goteborg, Sweden
J L Barker, Bethesda, MD, U S A
A. Björklund, Lund, Sweden
J. Bureš, Prague, Czechoslovakia
V. Chan-Palay, Cambridge, Mass, U S A
K. Fuxe, Stockholm, Sweden
G.L. Gerstein, Philadelphia, PA, U S A
T. Hökfelt, Stockholm, Sweden
J.P. Huston, Dusseldorf, W Germany
L. Iversen, Cambridge, U K
R.Y. Moore, La Jolla, CA, U S A
Shin-Ho Chung, London U K
D.F. Swaab, Amsterdam, The Netherlands
R.E. Zigmond, Cambridge, Mass, U S A

1979 Volume 1 in 4 issues
Subscription price US $ 67 50/Dfl 155 00 including postage

To ensure that you receive further information and/or a free specimen copy when available, please write to the **Promotion Manager** mentioning this advertisement

ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS

send your orders or requests for free specimen copies to

in the U S A and Canada
JOURNAL INFORMATION CENTER
Elsevier's Science Division
52 Vanderbilt Ave,
New York, NY 10017

in all other countries
ELSEVIER/NORTH-HOLLAND
BIOMEDICAL PRESS
P O. Box 211, 1000 AE, Amsterdam,
The Netherlands

The Dutch guilder price is definitive US $ prices are subject to exchange rate fluctuations

ERRATUM

THE NEUROANATOMY OF AMNESIA: A CRITIQUE OF THE HIPPOCAMPAL MEMORY HYPOTHESIS

by JAMES A. HOREL
Vol. **101**, 403-445

P. 411, lines 36-43. *Delete* 'Another way to make the task non-spatial . . . hippocampal animals have no deficit' and *substitute:*

'Hippocampal lesions also produce severe deficits on spatial reversals but not object reversals. In the spatial reversal task, the animal is first rewarded for choosing the left one of two identical objects. After it learns to do this, the rewarded side is reversed and it must then learn to respond to the object on the right. This reversal is repeated several times. The object reversal is a non-spatial version of the same task. The procedure is the same except that two different objects are used and the animal is trained to respond first to one object, then to the other. On each trial, the side upon which the objects appears varies randomly.

'Thus if the spatial aspect of these tasks is eliminated, hippocampal animals have no deficit . . .'

The Author and Editors regret the error.

Brain (1978), **101**, 569-589

HEMISPHERE FUNCTION AND BINOCULAR DEPTH PERCEPTION

by G. DANTA,[1] R. C. HILTON *and* D. J. O'BOYLE

(*From the Neurology Department, Manchester Royal Infirmary and the Department of Psychology, University of Manchester*)

INTRODUCTION

AN almost total loss of stereoscopic vision and depth perception is a highly unusual consequence of brain injury. Those patients described in the literature (Riddoch, 1917; Holmes and Horrax, 1919; Faust, 1947; Birkmayer, 1951; Critchley, 1953; Hécaen and de Ajuriaguerra, 1954; Hécaen and Angelergues, 1963), typically remarked that everything in the visual world seemed to lie in the same frontal plane and that objects no longer possessed visual depth or thickness. As a result, although a limited ability to distinguish whether objects are very near or very distant may be retained (Riddoch, 1917), relative or absolute localization in the sagittal plane becomes a matter of logical reasoning. For example, upon being asked to calculate the distance, from himself, of the opposing wall of the room in which he was seated, the patient described by Hécaen and Angelergues (1963) was constrained to multiply the number of intervening floor tiles by their apparent individual width in order to arrive at an answer. Less dramatic disorders of visual depth perception have, on the other hand, been reported rather more frequently (Badel, 1888; Pick, 1898; Anton, 1899; van Valkenburg, 1908; Bielschowsky, 1908; Smith and Holmes, 1916; Yealland, 1916; Poppelreuter, 1917/18; Holmes, 1918*a*, *b*; Riddoch, 1935; Brain, 1941; Paterson and Zangwill, 1944; Stengel, 1944; Symonds, 1945; Bender and Teuber, 1947, 1948; Martin, 1949; Best, 1952; Gooddy and Reinhold, 1952; Ettlinger, Warrington and Zangwill, 1957; Cogan, 1960, 1965; Cole, Schutta and Warrington, 1962; Hécaen and Angelergues, 1963; Godwin-Austen, 1965; Michel, Jeannerod and Devic, 1965), and range from a very severe impairment (Michel, Jeannerod and Devic, 1965) to a mere reduction in stereoacuity (Paterson and Zangwill, 1944).

In more than half of the reported patients, lesions involved both cerebral hemispheres (27 of 46 cases); they were confined to the right hemisphere in 11 and to the left in 4; the site of lesion was uncertain in 4 patients. In the majority of patients the site of lesion was determined clinically and only 11 patients had come to autopsy. In all cases impaired depth perception was accompanied by other symptoms of hemispheric dysfunction, the commonest being a visual field defect present in 35 of the 46 patients. It was recorded as absent in 8, and not alluded to in 3 patients.

---

[1] Present address: Neurology Unit, Canberra Hospital, ACT 2601 Australia.

Holmes (1918*b*) argued that the defects of visual localization observed in his patients could be directly attributed to the cerebral lesions affecting 'the local sign function of the retinæ'. This view that other associated signs are without necessary ætiological significance in the production of disordered depth perception has met with criticism, notably from Piéron (1927), and indeed, as Kleist (1934) has pointed out, problems of relative localization may, on occasions, be secondary to the presence of visual field defects or anomalous fixation. Nevertheless, the more recent literature tends to support the notion that disorders of depth perception may arise as a primary consequence of cerebral injury. For example, it seems improbable that the gross impairment of depth perception sustained by Symonds' (1945) patient, following injury to the right occipital region, was caused by the reduced range of convergence and the small scotomas in the left homonymous inferior quadrants which together constituted the only other discernible signs.

An analysis of actual or presumed sites of lesions within the hemispheres among the reported cases supports Holmes' (1918*b*) original remark that lesions within a region centred upon the posterior parietal lobe and extending into surrounding occipital and temporal gyri are especially implicated in the production of disordered visual depth perception. Nevertheless, the literature suggests that the possible involvement of other areas such as the medial portions of the occipital lobe (Holmes, 1918*b*; Ettlinger, Warrington and Zangwill, 1957) and the splenium of the corpus callosum (Holmes, 1918*b*; Mitchell and Blakemore, 1970) cannot be discounted, particularly in view of the absence of autopsy data in the majority of case reports.

Whilst bilateral lesions were implicated in the majority of instances, it has been repeatedly confirmed that unilateral lesions in either hemisphere may give rise to impairment in the contralateral hemifield. These findings led Brain (1941) to conclude that the neural mechanisms underlying visual localization are not subject to the dominance of one hemisphere. A number of subsequent studies lends support to this view. Hécaen and Angelergues (1963), for example, studied 215 patients with lesions posterior to the central sulcus and found that impaired depth perception, when it occurred, was not preferentially associated with unilateral lesions in one hemisphere rather than the other, but in fact more commonly followed bilateral lesions. Similarly, Lehmann and Wälchli (1975), on the basis of another group study, suggested that the laterality of a lesion was not of significance in determining performance on the Titmus stereotest.

However, in 1951, Zangwill, after briefly describing four patients, in all of whom a right-sided lesion was associated with mildly impaired depth perception in central vision, commented that 'such defects appear to bear a rather special relation to the parietal lobe of the minor hemisphere'. Several other cases of impairment in central vision following lesions thought to be restricted to the right hemisphere have been described (Symonds, 1945; Critchley, 1953; Ettlinger, Warrington and Zangwill, 1957). It is also of interest in this context that Cogan's (1965) first patient, who eventually suffered a biparietal lesion, complained of reaching beyond objects prior to the development of signs indicating involvement of the left hemisphere.

Birkmayer, also writing in 1951, reported that of 70 brain-injured patients with impaired depth perception, 53 (76 per cent) had a left-sided and 13 (19 per cent) a right-sided hemianopia. More recently, Carmon and Bechtoldt (1969) found that right hemisphere lesions produced marked deficits on a stereoscopic task using random letter stereograms, whereas patients with left hemisphere lesions performed at the level of neurologically intact controls. Using the same stimulus materials, Benton and Hécaen (1970) replicated this finding and also reported a reversal of the relationship in two left-handed subjects. Furthermore, similar conclusions of a right hemisphere dominance for stereopsis were drawn by Durnford and Kimura (1971) from a study of normal subjects using split-field tachistoscopic presentation of both random-dot stereograms and a two-rod apparatus.

This emerging picture of a right hemisphere dominance is, however, somewhat confused by several other studies. Cogan (1960), for example, briefly described a patient who complained of disordered depth perception in central vision and who had a tumour in the left parieto-occipital area. Similarly, Rothstein and Sacks (1972) found that greater impairment of performance on the Titmus stereotest was associated with unilateral parietal lesions on the left rather than on the right. Richards (1970), moreover, in a tachistoscopic study not specifically directed at this question of hemisphere dominance, found a greater probability of wide-field disparity detection following stimulus presentations in the right hemifield than in the left hemifield, in 75 normal subjects ranging between 5 and 70 years of age.

In the present study, we attempted to examine these questions further by testing the stereoacuity of a number of patients with focal lesions restricted to one hemisphere, using two different experimental procedures.

METHODS

1. *The 'Dropping Bead' (DB) Method*

This was based upon Hering's (1865) 'Fallapparat'. Facing the subject was a cubic box which was finished with a matt black exterior and matt white interior. Through a central aperture in one side, the subject saw the white back face diffusely lit by a fluorescent light which was fitted to the ceiling of the box and consequently was not directly visible. On a horizontally strung white cotton thread was centrally mounted a dark blue stationary bead one cm in diameter. Identical beads could be dropped up to 19·5 cm directly in front of or behind it through two moveable funnels fitted in a slot in the top face of the box.

The subject sat with his head held in a harness so that the stationary bead, on which he was asked to fixate throughout the experimental procedure, was at eye-level and 300 cm from the eyes. The room was darkened and the subject saw only the lighted aperture, the back face of the box and the stationary bead. Two plumb lines, situated 24 cm in front of, and behind, the stationary bead, were lowered and the position of the box was adjusted so that both lines, and the stationary bead between them, appeared to the subject directly in line as he gazed at the bead with both eyes. This position was checked by the experimenter who viewed the box from just above the subject's head. The plumb lines were then withdrawn. Before beads were dropped, the subject was given time to adapt to the constant level of uniform background illumination provided by the hidden fluorescent lighting. The floor of the box was thickly padded with cotton wool to eliminate auditory cues. Ten beads were dropped in random order at displacement distances of 1·5, 4·5, 7·5 and 10·5 cm both in front of, and behind, the stationary bead. The subject was asked to state each time whether he thought the bead fell in front of, or behind, the stationary bead, and to guess when uncertain. The number of errors was recorded at each of the distances, the range of which was extended by 3 cm intervals, if necessary, to a maximum distance of 19·5 cm, until the subject responded correctly on 95 per cent (19/20) trials. The duration of visible beadfall, through a vertical angle of 8·4 degrees, was 196 ms.

2. *The Haploscopic Method*

Two miniature bulbs (1·12 watts, powered by a DC stabilized source) were each mounted in a small box, each of which had a circular aperture 2 mm in diameter. The two boxes were mounted on an optical bench so that, at eye-level and at a distance of 250 cm from the eyes, the subject saw two lights side by side in the same frontal plane, one through, and one reflected by, a half-silvered mirror. Each light thus subtended an angle of 2·75 min of arc at the eye. Polaroid discs were fitted in front of the subject's eyes and in front of each light source so that the light on the right was seen only by the right eye, and the one on the left only by the left eye. When he looked at the light sources, the subject therefore perceived a single light located in space (fused dot) as a consequence of binocular fusion. The fused dot could be made to approach the subject by approximating the two light sources and to recede from him by separating them. The degree of separation of the lights was controlled by a dial calibrated in arbitrary units. This calibration was frequently checked. The position of the fused dot in depth could be related by the subject to an illuminated wire-mesh screen which itself presented no spatial cues, and which was mounted on the same optical bench.

The subject sat in a darkened room with his head held in a harness at a distance of 300 cm from the screen. He was first required to adjust the brightness of the screen until it was of the same intensity as that of the fused dot. The separation of the two light sources was then so adjusted that, to the subject, the fused dot appeared to lie directly below the screen in the same frontal plane. This was repeated ten times and a mean reading (x) calculated. The light source separation was then systematically varied about this mean separation (x) so that the fused dot appeared at random a given distance in front of, or behind, the screen at distances corresponding to 2, 6, 10 and 14 dial units. The subject was again forced to state on each trial whether the fused dot lay in front of, or behind, the screen and errors were recorded. Ten trials were run at each of the displacement distances and the range extended in intervals of 4 dial units, if necessary, until the subject responded correctly on 95 per cent (19/20) trials. The lights and screen were occluded from the subject's gaze between trials. A measure of the relationship obtaining between light-source separation (dial units) and subject-to-fused dot distance was derived by repeating the procedure outlined above for the calculation of x, at subject-to-screen distances of 290 and 310 cm for each subject.

SUBJECTS

Fifty-four patients with single focal lesions restricted to one cerebral hemisphere were examined: 26 patients had lesions in the right hemisphere and 28 had lesions in the left hemisphere. All patients were right-handed with the exception of two patients with left hemisphere lesions. Details of the age and sex of subjects are given in Table 1. The patients were studied during a period of eighteen months and were selected from the Neurological and Neurosurgical Departments according to a number of criteria: (i) signs and symptoms indicated a single lesion confined to one cerebral hemisphere; (ii) visual acuity was 6/9 6/9 (Snellen) or better; (iii) there was no clinical evidence of eye-movement disorder; (iv) patients were sufficiently well to co-operate reliably in the experimental procedure which lasted up to one-and-a-half hours. Consequently, relatively well patients, rather than those severely disabled, were studied.

TABLE 1. NUMBERS, AGES AND SEXES OF PATIENTS WITH RIGHT AND LEFT HEMISPHERE LESIONS AND OF CONTROL SUBJECTS

		Age (years)				*Sex*	
Subjects	*No.*	*Mean*	*SD*	*SE*	*Range*	*M*	*F*
Right hemisphere	26	49·6	12·82	2·51	18–73	20	6
Left hemisphere	28	47·1	12·37	2·34	14–70	18	10
All patients	54	48·3	12·53	1·71	14–73	38	16
Controls	51	43·1	13·19	1·85	19–71	31	20

No patient complained of any disturbance of his visual environment unless a field defect was present; or, in particular, of difficulty in judging distances.

From 32 patients, cerebral angiograms, air studies, brain scans or operative reports were available for more precise localization of the lesion. The extent of the lesions in these patients was traced independently onto plain skull radiographs by a radiologist. These traces were then superimposed on traces of average skull radiographs to produce composite diagrams of the approximate size and location of lesions in groups of patients (fig. 3).

Fifty-one subjects constituted the control group; 40 were examined using both test situations, and the remaining 11 using either one or the other. Forty-three patients were in hospital and 8 were normal subjects. None of the subjects had signs of ocular abnormality, neurological disorder or a history of squint or diplopia. Age and sex distributions of subjects are given in Table 1.

Neither patients nor control subjects had previously had any experience of similar or related procedures.

Visual acuity in each eye was determined by asking the subject to read the Snellen chart at a distance of 6 m. The interpupillary distance was measured with a ruler, as the subject fixated on a light source 300 cm distant. The mean was taken of two readings obtained independently by two observers. Phoria was determined in prism dioptres.

Method of Data Analysis

The data obtained with each test procedure consisted of the number of errors out of ten made by the subject at each of several distances behind and several distances in front of the reference point. We adopted the method of linear interpolation to extract a measure of stereoacuity from our 'constant stimuli' data. Results were graphed plotting the range of displacement (disparity) distances against the proportion of 'in front' responses at each of these distances. The near (proximal) and far (distal) thresholds (T_n and T_f) were arbitrarily set at the 0·75 and 0·25 probability levels, respectively, indicating the displacement distance at which the falling bead or 'fused dot' was correctly perceived as being in front or behind the reference point with a probability of 0·75. These values may be obtained by using the following expression (Corso, 1970):

$$T_n = Sb + (Sa - Sb)\,(C - Pb)/(Pa - Pb) \text{ cm}$$

where T_n = the proximal (or near) threshold
Sa = the stimulus value immediately above T_n
Sb = the stimulus value immediately below T_n
Pa = the proportion of 'nearer' judgements for the stimulus value immediately above T_n
Pb = the proportion of 'nearer' judgements for the stimulus value immediately below T_n
C = the proportion of judgements defining the threshold criterion.

The linear thresholds (T_n and T_f), whose sum gave the 'interval of uncertainty' (IU), were then converted to thresholds of angular disparity (η_n and η_f) and were calculated from both the haploscopic and the dropping bead data for each subject (fig. 1).

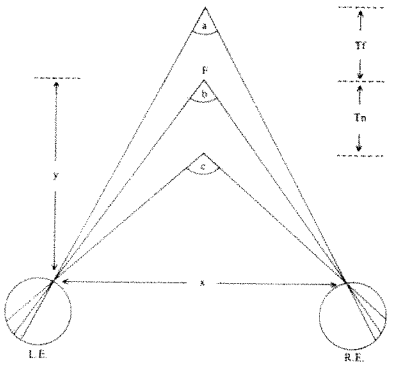


FIG. 1. Calculation of angular thresholds. x = interpupillary distance; y = observation distance to fixation or reference point F; T_f, T_n = far and near linear thresholds. For small angles:

$$\text{Far angular threshold } (\eta_f) = b - a = \frac{xT_f}{y^2 + yT_f} \times \frac{648{,}000}{\pi} \text{ s of arc.}$$

$$\text{Near angular threshold } (\eta_n) = c - b = \frac{xT_n}{y^2 - yT_n} \times \frac{648{,}000}{\pi} \text{ s of arc.}$$

In the case of the haploscopic data, the displacement distances in cm corresponding to dial units of 2, 6, 10 and 14 were calculated from the individual calibration data at the subject-to-screen distances of 290 and 310 cm.

Among control subjects, group mean IU values did not differ significantly between any of the four visual acuity groups on either of the two methods used for assessing stereoacuity (Table 2). Consequently, for each method, data from all control subjects were pooled to yield an overall mean IU and standard deviation. χ^2 for goodness-of-fit to a normal distribution revealed low P values for both sets of IU data (DB, $P = 0{\cdot}02$; haploscopic, $P = 0{\cdot}004$). Of a number of transformations, the log transformation in both cases yielded the highest P values (DB, $P = 0{\cdot}72$; haploscopic, $P = 0{\cdot}04$) and was therefore used to set up 'tolerance limits of abnormality'. According to either method, we chose to accept a patient as having abnormal stereoacuity if the log IU value exceeded the control mean log IU value by more than three standard deviations.

TABLE 2. RESULTS AMONG CONTROL SUBJECTS IN S OF ARC

	Dropping bead		*Haploscopic*	
Visual acuity	*n*	*Mean IU*	*n*	*Mean IU*
6/5–6/6	14	45 (18)	14	63 (31)
6/6–6/6	12	49 (31)	9	60 (39)
6/6–6/9	9	41 (9)	10	67 (27)
6/9–6/9	14	56 (35)	9	67 (25)

IU = Interval of uncertainty. Numbers in brackets = standard deviations.

For several subjects, however, it was not possible to calculate IU values. In the case of the haploscopic procedure, 7 patients were completely unable to fuse the two images of the haploscopically presented stimuli (NF) and 10 patients, having been able to fuse, proved incapable of discriminating the position of the fused light with respect to the reference object (ND). Such performance was considered abnormal because of the complete absence of such difficulties among control subjects, and the results of these patients were therefore included in the Tables and analyses among those with abnormal IU values.

IU values derived from the use of the DB procedure were also incalculable for two patients with right hemisphere lesions. Both patients made very few or no errors when beads were dropped behind the stationary bead, but were still making 80 per cent of errors at a dropping bead displacement distance, in front, of 19·5 cm. Such performance was also considered abnormal in view of its singularity.

RESULTS

Control subjects were allocated on the basis of visual acuity to one of four groups: 6/5 6/5, 6/6 6/6, 6/6 6/9 and 6/9 6/9. Table 2 shows mean IU values obtained from experiments using both methods. In neither the dropping bead nor the haploscopic results did the IU values differ significantly among the visual acuity groups (Mann-Whitney U test). Calculation of the Spearman rank correlation coefficient (r_s) and associated t-value (Siegel, 1956), revealed that stereothreshold values derived from the dropping bead procedure were correlated at a low and statistically insignificant level with those derived from the haploscopic procedure ($r_s = 0{\cdot}139$; $t = 0{\cdot}827$; $df = 38$; $P > 0{\cdot}10$).

Results of the dropping bead procedure among patients are presented in Table 3. χ^2 test reveals no significant difference in performance between the two hemisphere groups ($\chi^2 = 1{\cdot}449$; $df = 1$).

TABLE 3. INCIDENCE AMONG PATIENTS OF ABNORMAL VISUAL DEPTH PERCEPTION AS ASSESSED BY THE TWO METHODS

	Dropping bead method		*Haploscopic method*	
Subjects	*Proportion*	*Percentage*	*Proportion*	*Percentage*
Left hemisphere	4/25	16	5/24	21
Right hemisphere	9/26	35	16/24	67
Controls	0/49	0	0/42	0

Table 3 also shows the corresponding results for the haploscopic task. Two-tailed χ^2 indicates that the respective performances of the two hemisphere groups differ significantly on this test ($\chi^2 = 8{\cdot}466$; $df = 1$; $P < 0{\cdot}01$). The supposition that this difference might simply be due to a significant age difference between the two hemisphere groups has no statistical support ($t = 0{\cdot}449$; $df = 46$).

Table 4 shows the proportion of patients in each hemisphere group who, on the haploscopic task, could not fuse the light sources (NF) or, having fused them, could not discriminate the position of the fused light (ND). Construction of 2×2 contingency tables and use of χ^2 showed that only in the latter case (ND) were patients distributed significantly asymmetrically among the two hemisphere groups, and then only according to a one-tailed test (NF: $\chi^2 = 2{\cdot}676$; df = 1. ND: $\chi^2 = 3{\cdot}158$; df = 1; $P < 0{\cdot}05$, one-tailed test). If, however, the NF and ND data are pooled, then a clearly significant difference between the two hemisphere groups is apparent ($\chi^2 = 9{\cdot}108$; df = 1; $P < 0{\cdot}01$, two-tailed test).

TABLE 4. COMPARISON OF HEMISPHERE GROUPS WITH REFERENCE TO PROBLEMS OF FUSION AND DEPTH DISCRIMINATION ON THE HAPLOSCOPIC TASK

	Fusion impossible		*Fusion possible but no depth discrimination*		*No fusion or depth discrimination*	
Subject	*Percentage of total*	*Percentage of abnormal*	*Percentage of total*	*Percentage of abnormal*	*Percentage of total*	*Percentage of abnormal*
Left hemisphere (n = 24)	4 (1/24)	20 (1/5)	8 (2/24)	40 (2/5)	13 (3/24)	60 (3/5)
Right hemisphere (n = 24)	25 (6/24)	38 (6/16)	33 (8/24)	50 (8/16)	58 (14/24)	88 (14/16)

In Table 5 the results are set out in a different way. The last two columns show the proportion of subjects who, having produced abnormal results on one task, also produced abnormal results on the other. Use of Fisher's exact probability test (Siegel, 1956) on 2×2 contingency tables constructed from columns 'normal DB/abnormal DB' and rows 'normal haploscopic/abnormal haploscopic' revealed no significant association between results of the two tests for the left hemisphere group ($P = 0{\cdot}194$). However, a significant association (one-tailed test) between respective performance on the two tasks was revealed for the right hemisphere group ($P = 0{\cdot}033$), largely due to the fact that all right hemisphere patients who produced abnormal results on the DB task also did so on the haploscopic task.

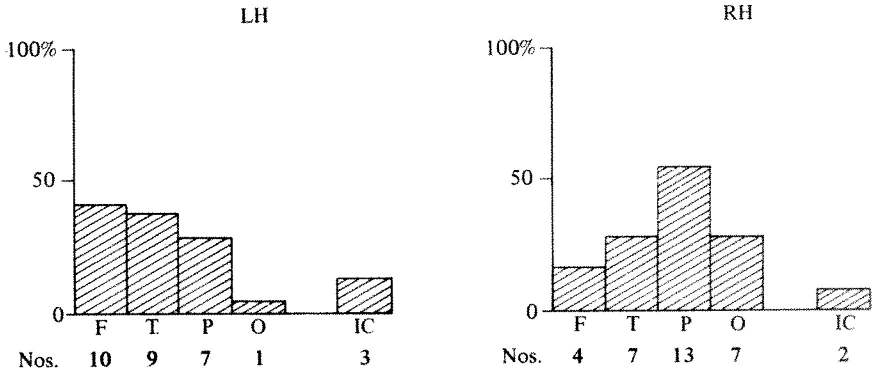
TABLE 5. COMPARISON OF HEMISPHERE GROUPS ON RESULTS OF THE TWO TASKS

	Abnormal on dropping bead	*Abnormal on haploscopic*	*Abnormal on one or the other*	*Abnormal on both*	*Abnormal of both/ abnormal on DB*	*Abnormal on both/ abnormal on haploscopic*
Left hemisphere	16% (4/25)	21% (5/24)	27% (7/26)	9% (2/23)	50% (2/4)	40% (2/5)
Right hemisphere	35% (9/26)	67% (16/24)	69% (18/26)	29% (7/24)	100% (7/7)	44% (7/16)

Apparent discrepancies in some figures due to not all subjects being tested by both methods.

Fig. 2 is based on clinical assessment and shows the incidence of involvement of each of the four hemispheric lobes and of the internal capsule for each hemisphere group. The sum of all columns in each histogram totals more than 100 per cent because some lesions implicated more than one lobe. Whilst we are aware of the limitations of cerebral localization based upon clinical evidence, it is apparent that, within the left hemisphere group, there is a skew towards more anterior lesion placements and, within the right hemisphere group, a skew towards more posterior placements. This asymmetry arose largely as a result of excluding patients who, because of a significant dysphasia, were not able to participate adequately in the experimental procedure.

Haploscopic Task



Dropping Bead Task

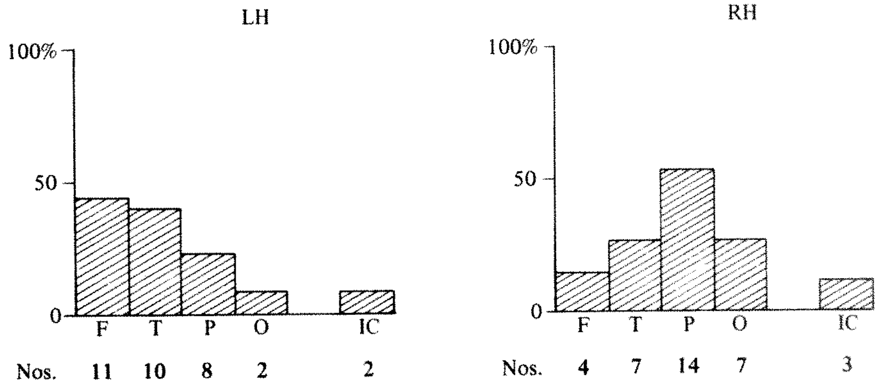


FIG. 2. Number of lesions clinically implicating the frontal (F), temporal (T), parietal (P) or occipital (O) lobes or the internal capsule (IC), expressed as a percentage of total number of patients with left and right hemispheric lesions studied by each method.

In 32 cases it was possible to localize the site of a hemispheric lesion more accurately from investigative procedures as described earlier. The composite diagrams derived from these procedures are shown in fig. 3.

Fig. 4 was derived from the lesion data of all 54 patients and shows, for each task and for each hemisphere, the number of times a lesion implicating a particular

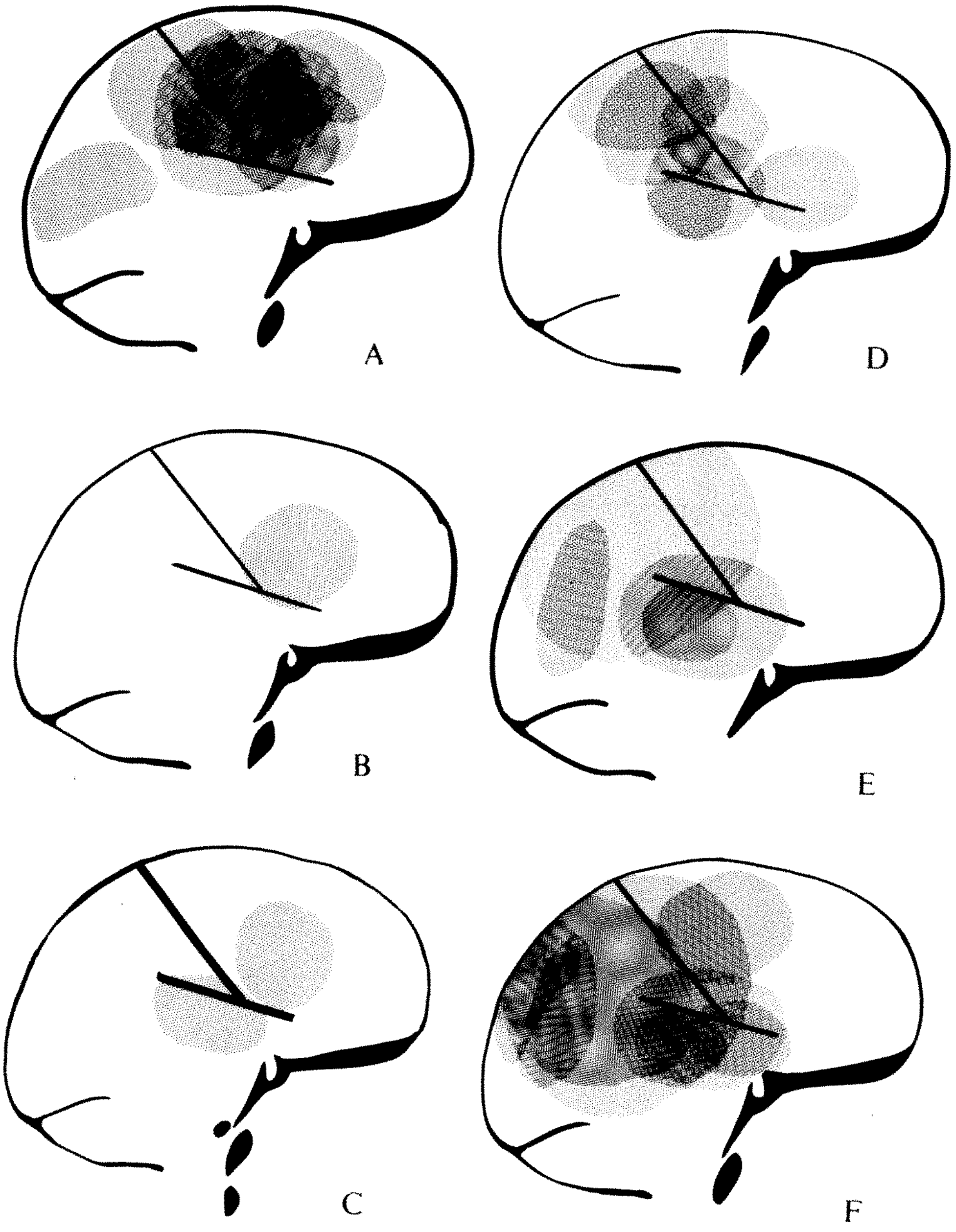
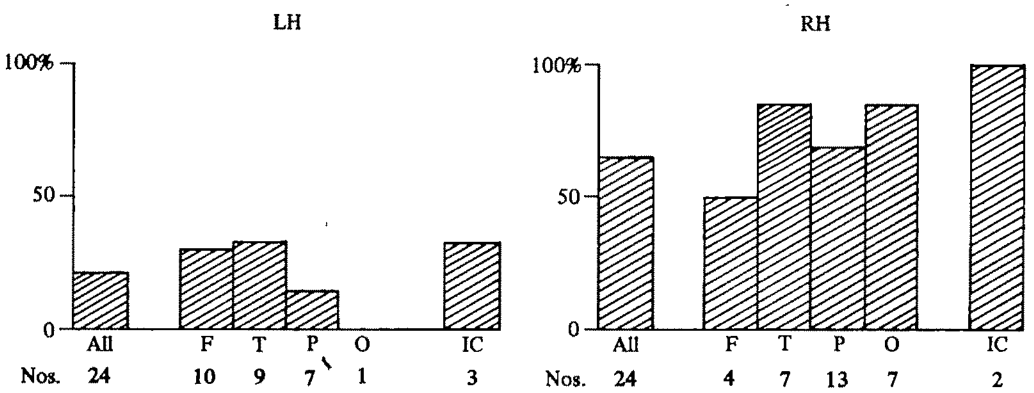


FIG. 3. Approximate extent and location of lesions, whose numbers are bracketed, superimposed on lateral skull x-rays. A–C = left, D–F = right hemisphere. A, D: normal stereopsis (11, 6); B, E: abnormal on dropping bead test (1, 4); C, F: abnormal on haploscopic test (2, 8).

lobe or the internal capsule was associated with abnormal performance. This datum is expressed as a percentage of the total number of lesions implicating that lobe in order to compensate to some extent for the asymmetrical distribution of lesions within the two hemisphere groups.

Haploscopic Task



Dropping Bead Task

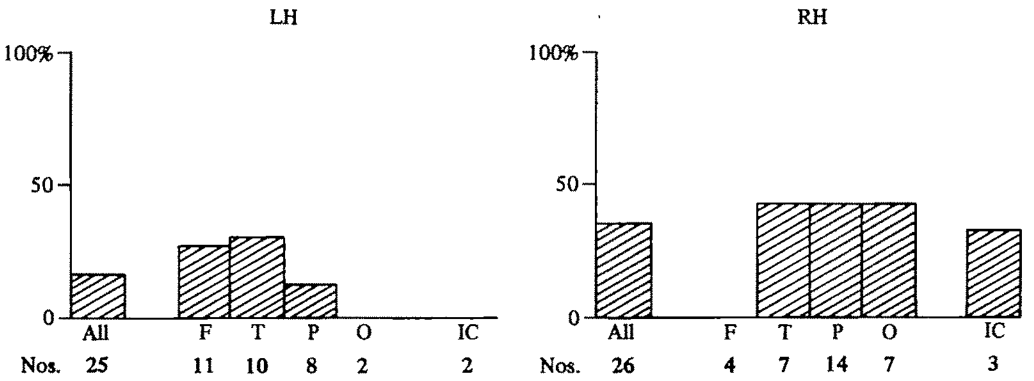


FIG. 4. Percentage of patients performing abnormally on the two tests out of all patients with clinical involvement of the frontal (F), temporal (T), parietal (P) or occipital (O) lobes or the internal capsule (IC).

Damage to the primary visual projection pathway, indicated by the presence of field defects, was present in 10 subjects, 9 of whom had abnormal stereopsis according to one or other of the two tasks. Examination of figs. 1 and 3 reveals, with this exception, no simple relationship between site of lesion and stereoscopic abnormality and that such impairment is not invariantly associated with damage within any single lobe in either hemisphere.

No difference in the incidence of abnormalities in stereoacuity could be shown between any of the following patient group pairs, the separation having been made on clincial grounds: (i) neurological signs present *vs* signs absent; (ii) duration of history <1 yr *vs* duration >1 yr; (iii) cerebral tumours *vs* cerebral infarcts; (iv) left hemisphere lesions: past or present dysphasia *vs* no dysphasia; (v) intracranial hypertension *vs* no hypertension; (vi) extracerebral (meningiomas, subdurals) *vs* intracerebral lesions.

The details included in Tables 3–5 inclusive and figs. 2–4 inclusive concern right-handed patients only. The two left-handed patients with left hemisphere lesions were omitted from analyses concerning the comparison of the two hemisphere groups. Both these patients performed within control limits on each of the two tasks.

DISCUSSION

A large proportion of our patients with focal lesions of the cerebral hemispheres were found to have impaired stereopsis, confirming the views expressed by Poppelreuter (1917/18) and by Birkmayer (1951) that damage to the hemispheres frequently disturbs stereoscopic perception. That none of our patients, even when specifically asked, expressed any difficulty in judging visual depth or distance in everyday life argues that depth cues other than horizontal retinal disparity adequately compensated for their defect in stereoacuity. Indeed, varying degrees of stereoscopic abnormality are to be found in a certain proportion of the 'normal' population (Richards, 1970). Therefore, unless an individual has some habitual, perhaps occupational, need for the precision in relative depth perception which stereopsis affords, some degree of impairment may well go unnoticed.

One criterion for the selection of patients was good visual acuity and the absence of oculomotor disorders. It is possible that some may have had impairment of convergence too small to be detected clinically, but large enough to impair fine stereopsis. However, it is unlikely that hemispheric lesions could account for the high incidence of stereoscopic abnormalities merely by way of slight impairment of convergence.

Disordered stereopsis did not correlate with the presence of sensory or motor signs in the limbs, the presence of dysphasia, raised intracranial pressure, length of history of the hemispheric disorder, or the ætiology of the lesion. It did, however, correlate with the presence of visual field defects, since 9 of 10 patients with a field defect had abnormal stereopsis. These findings conform to those contained in published reports and indicate that, with the exception of visual field defects, disordered stereopsis is not necessarily related to the presence of other ocular or neural signs or symptoms.

Although field defects are commonly associated with disordered depth perception, this is not invariable. Teuber, Battersby and Bender (1960), for example, described a patient (A29) with normal stereoscopic vision in the presence of tunnel vision following a lesion of the left hemisphere. Similarly, one of our patients who had a complete left homonymous hemianopia with macular sparing at the time of testing, had normal stereoacuity as determined by both methods. These considerations support Holmes' (1918*b*) view that when hemispheric lesions give rise to disordered depth perception, any associated signs, including visual field defects, are without necessary ætiological significance in its production.

The fact that in many of our patients with abnormal stereoscopic vision there was no clinical evidence of disturbance of the primary visual pathway and that, in several instances, the lesion was remote from it, is of interest in view of the discovery of binocularly-driven cells in area 17 in the cat (Barlow, Blakemore and Pettigrew, 1967) and area 18 in the monkey (Hubel and Wiesel, 1970) which might serve as a substrate for binocular single vision and depth discrimination. Although direct electrophysiological evidence is not yet available, psychophysical experiments with human subjects have indicated the probable existence, within the human brain, of disparity-detecting neurons similar to those found in the cat and monkey (Mitchell and Baker, 1973). Although these studies indicate that the integrity of the human visual cortex may be a necessary prerequisite for normal stereopsis, our data suggest that it is not a sufficient one and that neural mechanisms in other areas of the brain, including regions lying outside the occipital lobes, have a significant role to play.

We found differing modes of abnormal performance in the haploscopic task (Table 4). Seven patients were totally unable to fuse the images of the two light sources or to localize the diplopic images, in depth, with respect to the screen. Of these patients, only 2 had lesions implicating the occipital lobes. Although there is evidence for binocular interaction at the level of the lateral geniculate nucleus (Sanderson, Darian-Smith and Bishop, 1969), binocular fusion is generally considered to be a cortical process and according to modern neurophysiological theory is subserved by mechanisms within the striate cortex (Bishop, 1973). Our data suggest that fusion may be disrupted by lesions outside the occipital lobes in areas which are presumably involved in processing subsequent to initial fusion in the striate cortex. However, in the absence of data derived from the use of other tests of fusional ability, it remains unclear whether the absence of fusion on the haploscopic task reported by these patients represents a severe impairment of stereoscopic perception or conforms to a qualitatively different abnormality of visual function. Information in the clinical literature concerning this issue seems singularly lacking. Although disorders of fusion may be common following traumatic head injury (Neely, 1947; Wade, 1965; Doden and Bunge, 1965; Hart, 1969), and several authors have briefly described difficulties of fusion in the stereoscope within the context of wider-ranging neurological case reports (Bender and Teuber, 1947/48; Michel, Jeannerod and Devic, 1965), we are unaware of any published studies concerned directly with the effect of focal brain damage on binocular fusion.

A second mode of abnormal performance on the haploscopic task was represented by 10 patients who, having fused the light sources, were then totally unable to discriminate the depth of the fused image with respect to the screen (Table 4). The occipital lobes were implicated in only 3 of these patients. This suggests that the neural processes underlying binocular single vision, and binocular depth discrimination, might to some degree be functionally dissociable. A related disturbance appears to have been described by Symonds (1945) whose patient, although able to fuse two stereoscopically-presented scenes of a landscape, was unable to discriminate the relative positions in depth of the objects and features depicted therein.

Such considerations do not arise with respect to the dropping bead procedure in which, as for the remaining patients abnormal on the haploscopic task, abnormal performance was defined in terms of an elevated stereothreshold; with two exceptions. Two patients with lesions in the right hemisphere made very few errors when beads were dropped behind the stationary bead, but were unable to discriminate when beads were dropped in front. Richards (1970) has argued that, in the human visual system, there are three distinct populations of disparity-specific cells subserving the detection of, respectively, convergent, divergent and zero disparities, and that in a proportion of the normal population, one or more of these classes of cell may be absent or non-functional. It is therefore tempting to conjecture that, in these two patients, neural mechanisms underlying the detection of convergent disparities may have been selectively disrupted by the lesions. However, had this simply been the case, we should have expected, in a two-choice forced discrimination procedure, that convergent disparities would have been correctly identified, by inference, as not being divergent disparities. The exact nature of the deficit in these two patients therefore remains unclear as does the question of whether the three classes of cells postulated by Richards may be differentially affected by focal brain lesions.

The haploscopic data (Tables 3 and 4) indicate that abnormal stereopsis was more common among patients with right hemisphere lesions. A similar directional trend is apparent in the dropping bead data although the difference between the hemisphere groups was not statistically significant. Whilst these results are consistent with those from other clinical group studies suggesting a right hemisphere 'dominance' for stereopsis (Birkmayer, 1951; Carmon and Bechtoldt, 1969; Benton and Hécaen, 1970), it might be argued that these data may be explained more simply and without necessary recourse to a hypothesis couched in terms of hemispheric functional asymmetry.

Lehmann and Wālchli (1975), for example, having shown that intellectual impairment may cause a significant decrement in performance on the Titmus stereotest, suggested that the pattern of results outlined above may be related to a predominance of intellectually impaired patients among the right hemisphere groups. This might commonly arise in group studies, they surmise, because left hemisphere cases tend to present clinically earlier than 'equivalent' right hemisphere cases because of impairments of speech and of the use of the preferred hand, and because severe left hemisphere cases will tend to be excluded from experimental study in view of the difficulties posed by dysphasia. Thus they point out that the mean ages of the right hemisphere groups in the experiments described by Carmon and Bechtoldt (1969) and by Benton and Hécaen (1970) were significantly higher than those of the corresponding left hemisphere groups.

Although we do not have any data directly bearing on this matter, we believe that it is unlikely that our results are explicable in these terms for two reasons. First, the mean ages of our two hemisphere groups did not significantly differ. Secondly, our criteria for the selection of patients naturally screened out those with relatively more severe CNS impairment who might consequently have been expected to have had significant intellectual impairment.

A related, and possibly more substantial, explanation is suggested by the asymmetrical distribution of lesions within the two hemispheres (fig. 2), especially since published case studies indicate a special role for the parieto-occipital area in spatial localization.

Such an asymmetry is likely to occur in any hemisphere group study unless particular attention is paid to matching lesion sites across groups. It is therefore unfortunate that incomplete details of sites of lesions are given by Benton and Hécaen (1970) and none at all by Carmon and Bechtoldt (1969) especially as both studies used small groups of patients (12 or fewer for each hemisphere group). Significantly, Hécaen (1975) in a further and unpublished investigation, using the same stimulus materials and methods, found no significant differences in performance between two hemisphere groups consisting of equivalent numbers of pre- and post-Rolandic lesions (RH: pre-R=11; post-R=14. LH: pre-R=14; post-R=14). Hécaen and Angelergues (1963) had, in fact, reported earlier similar results following the examination of a large number of patients with post-Rolandic lesions (LH=87; RH=104; bilateral=24) using several apparently nonquantitative tests of stereoscopic vision and depth perception. Rothstein and Sacks (1972) on the other hand, restricting their attention to parietal lesions, suggested a left hemisphere dominance for stereopsis, although their use of very small patient groups (LH=2; RH=8) must render such conclusions precipitate.

The results of these investigations indicate that clinical studies of groups unmatched with respect to site of lesion may have only a limited, and perhaps misleading, bearing on the question of whether or not depth perception and stereopsis is a function to which hemisphere dominance applies. Bearing in mind that the present study is not, of course, exempt from this stricture, the shapes of the histograms in fig. 2 suggest that lesions within the temporal, parietal and occipital lobes in the right hemisphere are of greater consequence in the production of impaired stereopsis than lesions within the equivalent areas in the left hemisphere, especially with respect to the dropping bead task, than lesions within the frontal lobes of the right hemisphere. On the other hand, lesions in the left hemisphere which are associated with such impairment appear to lie preferentially in the frontal and temporal regions. We should stress, however, that conclusions drawn from fig. 4 must be considered extremely tentative in view of the fact that several of the columns in the histograms were constructed on the basis of very small samples and because in many cases lesions were not restricted to a single lobe.

Our two left-handed patients with left-sided lesions performed normally on both tasks, in contradistinction to the two sinistrals described by Benton and Hécaen (1970). One, with a left hemisphere lesion, performed defectively on the random-letter stereogram task, whereas the other, with a right-sided lesion, performed erroneously. Although the number of patients is clearly too small to allow us to draw any useful conclusions concerning hemisphere dominance for stereopsis in sinistrals, especially as it is known that hemisphere organization in sinistrals is not simply a mirror-image of that found in dextrals (Gloning, Gloning, Haub and Quatember, 1969), the contradictory nature of these results emphasizes the need, in hemisphere dominance studies, for details of manual laterality. Such information is lacking not only in the majority of clinical case reports, but also in many of the group studies (Carmon and Bechtoldt, 1969; Durnford and Kimura, 1971; Lehmann and Wälchli, 1975).

The clinical case literature and the split-field tachistoscopic studies of normal individuals do not appear to add significantly to our understanding of this problem. Although impaired depth perception in central vision has been more commonly reported to follow lesions in the right rather than lesions in the left hemisphere, the total number of such case reports is small and only in one instance (Ettlinger, Warrington and Zangwill, 1957) was there confirmation at autopsy that the lesion was unilateral. The report of superior depth perception and stereopsis in the left visual field of normal subjects by Durnford and Kimura (1971) appears to be contradicted by the results of a similar study by Richards (1970) and is not supported by our own unpublished data. Unfortunately, there are no published accounts of experiments of this nature conducted using split-brain patients.

Of the several factors which have contributed to the present state of confusion, one of the most important concerns the large variety of tests which have been used by different investigators to assess stereopsis and depth perception. The degree to which the results derived from the use of these varying procedures are directly comparable is far from clear. It is known, for instance, that the magnitude of stereothresholds will vary with the nature of the tests and the psychophysical procedures used to determine them. The lack of a significant rank order correlation between the respective performance of our control subjects on the dropping bead and haploscopic procedures is consistent with this fact. Furthermore, the neural mechanisms underlying normal performance on the various tests are certainly not, in each case, identical. Table 5 shows that the performance of our patients with brain lesions was by no means the same on each of the two tasks, and, in fact, of those patients who were tested on both tasks and were abnormal according to one or the other, only 39 per cent (9/23) were abnormal according to both. Similar findings were reported in 1951 by Birkmayer who tested a large number of patients with brain damage on each of four standard tests of visual depth perception and repeatedly found that individual performance varied markedly with the type of test. Several patients, for example, performed normally on one test, only to fail completely on another. Fewer patients performed abnormally on the dropping bead procedure than on any of the other three tests, suggesting, as Birkmayer points out, that distances of moving objects are more readily and accurately perceived than of stationary ones.

That cerebral lesions may differentially affect depth discrimination of moving and stationary objects is illustrated by Case 8 (M.P.) described by Birkmayer (1951). The patient had 'good depth perception' when tested by the dropping bead procedure, and yet described that objects more than about 1·5 m distant appeared almost in one plane. He found that head movements helped depth discrimination and that, whereas he could not discriminate depth or judge distances of stationary objects, this difficulty waned when objects were in motion, to the extent that he could play hockey and basketball adequately.

Further evidence for the complexity of functional organization of neural mechanisms subserving depth and distance perception, and for the ways they may become deranged by cerebral disorders, is afforded by the remarkable patient described by Kramer (1970), who lost the ability to perceive depth and perspective in drawings and pictures, but who had normal stereoscopic vision and no difficulty perceiving depth or distance of real objects.

It seems, then, that normal visual depth perception does not, as some authors appear to imply, depend simply upon the integrity of a unitary brain mechanism discretely localized within a particular area of one hemisphere, but rather upon the hierarchical organization of a number of logically discrete but functionally interrelated neural mechanisms which may involve widespread areas of the brain. The exact nature of the impairment produced by a particular lesion will therefore depend upon the level at which this organization is disrupted. Significant advances in our clinical understanding of these issues will depend in turn upon the degree to which the currently available tests of depth perception and stereopsis are capable of selectively addressing these different neural mechanisms.

SUMMARY AND CONCLUSIONS

Binocular depth perception was measured in 26 patients with right and 28 patients with left hemisphere lesions using two methods. There was no simple correlation between the results obtained by the two methods. Abnormalities on one or the other method were found among 27 per cent of the left hemisphere group and 69 per cent of the right hemisphere group. Despite this high incidence, no patient had subjective impairment of visual depth perception. Among clinical signs, only the presence of visual field defects correlated with abnormalities of

visual depth perception. One patient, however, who had a complete left homonymous hemianopia with macular sparing, had normal stereoacuity as assessed by both methods. Lesions clinically not implicating the primary visual pathways and situated remote from the occipital lobes often impaired visual depth perception.

On the basis of these findings, and those reported by other workers, it is concluded that:

(1) disorders of stereopsis and visual depth perception can be demonstrated in a large proportion of patients with focal cerebral hemispheric lesions, but only uncommonly does a hemispheric lesion give rise to a symptomatic and significantly disabling disorder of depth perception;

(2) although visual field defects are common in patients with hemispheric lesions and disordered depth perception, there is no evidence that any particular neural or ocular signs are necessarily of ætiological significance in the production of the disorder;

(3) neural processes underlying binocular single vision (fusion) and binocular depth discrimination may be functionally dissociable;

(4) neural mechanisms in areas outside the occipital lobes and primary visual projection systems seem to play an important role in normal stereopsis; visual depth perception seems not to depend on the integrity of a unitary brain mechanism discretely localized within a particular area of one hemisphere, but rather upon the hierarchical organization of a number of logically discrete but functionally interrelated neural mechanisms which may involve widespread areas of the brain;

(5) the question of whether or not depth discrimination and stereopsis is a function to which hemisphere dominance applies is as yet unsettled. On available evidence it cannot be unequivocally stated that the right hemisphere is dominant for stereopsis;

(6) interpretation of systematic studies of stereoacuity and visual depth perception is made difficult by the fact that results derived from different tests are often not comparable.

ACKNOWLEDGEMENTS

The authors are grateful to Professor Brian Pullen for devising the haploscopic procedure and to the Department of Medical Physics, Manchester Royal Infirmary, for constructing the apparatus. Dr. Ian Isherwood, Neuroradiologist, helped to trace the extent of lesions from angiograms, air studies and brain scans onto outlines of lateral skull x-rays, and Dr. Walter Boyd transposed these onto outlines of 'average' skull x-rays. The Department of Medical Illustration, Stoke-on-Trent, kindly prepared fig. 1.

ADDENDUM

After this paper had been submitted, Hamsher (1978) reported the effects of unilateral hemisphere damage on performance of each of 3 tests of stereoscopic function including random-letter stereograms. He concluded that the right hemisphere is dominant for global, but not local, stereopsis and that intellectual impairment may be ruled out as a potential artefact in earlier studies.

REFERENCE

HAMSHER, K. DE S. (1978) Stereopsis and unilateral brain disease. *Investigative Ophthalmology and Visual Science*, **17**, 336-343.

REFERENCES

ANTON, D. G. (1899) Beiderseitige Erkrankung der Scheitelgegend des Grosshirnes. *Wiener Klinische Wochenschrift*, **12**, 1193-1199.

BADEL (1888) Contribution à l'étude des cécités psychiques: alexie, agraphie, hémianopsie inférieure, trouble du sens de l'espace. *Archives d'Opthalmologie, Paris*, **8**, 97-117.

BARLOW, H. B., BLAKEMORE, C. and PETTIGREW, J. D. (1967) The neural mechanism of binocular depth discrimination. *Journal of Physiology, London*, **193**, 327-342.

BENDER, M. B. and TEUBER, H. L. (1947 and 1948) Spatial organisation of visual perception following injury to the brain. *Archives of Neurology and Psychiatry*, **58**, 721-739; **59**, 39-62.

BENTON, A. L. and HÉCAEN, H. (1970) Stereoscopic vision in patients with unilateral cerebral disease. *Neurology, Minneapolis*, **20**, 1084-1088.

BEST, F. (1952) Zur Frage der Seelenblindheit. *Archiv für Psychiatrie und Nervenkrankheiten vereinigt mit Zeitschrift für die gesamte Neurologie und Psychiatrie*, **188**, 511-543.

BIELSCHOWSKY, A. (1908) Über ungenwöhnliche Erscheinungen bei Seelenblindheit. *Berichte der deutschenophthalmologischen Gesselschaft*, **35**, 174-184.

BIRKMAYER, W (1951) *Hirnverletzungen*. Vienna: Springer-Verlag.

BISHOP, P. O. (1973) Neurophysiology of binocular single vision and stereopsis. In: *Handbook of Sensory Physiology*. Edited by R. Jung. Berlin: Springer-Verlag. Volume VII/3, Part A, pp. 256-305.

BRAIN, W. R. (1941) Visual disorientation with special reference to lesions of the right cerebral hemisphere. *Brain*, **64**, 244-272.

CARMON, A. and BECHTOLDT, H. P. (1969) Dominance of the right cerebral hemisphere for stereopsis. *Neuropsychologia*, **7**, 29-39.

COGAN, D. G. (1960) Hemianopia and associated symptoms due to parietotemporal lobe lesions. *American Journal of Ophthalmology*, **50**, 1056-1066.

—— (1965) Ophthalmic manifestations of bilateral non-occipital cerebral lesions. *British Journal of Ophthalmology*, **49**, 281-297.

COLE, M., SCHUTTA, H. S. and WARRINGTON, E. K. (1962) Visual disorientation in homonymous half-fields. *Neurology, Minneapolis*, **12**, 257-263.

CORSO, J. F. (1970) Psychophysical methods. In: *The Experimental Psychology of Sensory Behaviour.* London: Holt, Rinehart and Winston, pp. 219-260.

CRITCHLEY, M. (1953) *The Parietal Lobes.* London: Arnold, p. 329.

DODEN, W. and BUNGE, H. (1965) Fusionsstörungen nach Schädelhirntraumen. *Klinische Monatsblätter für Augenheilkunde*, **146**, 548-553.

DURNFORD, M. and KIMURA, D. (1971) Right hemisphere specialisation for depth perception reflected in visual field differences. *Nature, London*, **231**, 394-395.

ETTLINGER, G., WARRINGTON, E. and ZANGWILL, O. L. (1957) A further study of visual spatial agnosia. *Brain*, **80**, 335-361.

FAUST, C. (1947) Ueber Gestaltzerfall als Symptom des parieto-occipitalen Uebergangsgebietes bei doppelseitiger Verletzung nach Hirnschuss. *Nervenarzt*, **18**, 103-115.

GLONING, I., GLONING, K., HAUB, G. and QUATEMBER, R. (1969) Comparison of verbal behaviour in right-handed and non-right-handed patients with anatomically verified lesion of one hemisphere. *Cortex*, **5**, 41-52.

GODWIN-AUSTEN, R. B. (1965) A case of visual disorientation. *Journal of Neurology, Neurosurgery and Psychiatry*, **28**, 453-458.

GOODDY, W. and REINHOLD, M. (1952) Some aspects of human orientation in space. *Brain*, **75**, 472-509.

HART, C. T. (1969) Disturbances of fusion following head injury. *Proceedings of the Royal Society of Medicine*, **62**, 704-706.

HÉCAEN, H. (1975) Personal communication.

—— and ANGELERGUES, R. (1963) *La Cécité Psychique.* Paris: Masson et Cie.

—— and DE AJURIAGUERRA, J. (1954) Balint's syndrome (psychic paralysis of fixation) and its minor forms. *Brain*, **77**, 373-400.

HERING, E. (1865) Die Gesetze der binocularen Tiefenwahrnehmung. *Archiv der Anatomie and Physiologie, Liepzig*, **40**, 152-165.

HOLMES, G. (1918*a*) Disturbances of vision by cerebral lesions. *British Journal of Ophthalmology*, **2**, 353-384.

—— (1918*b*) Disturbances of visual orientation. *British Journal of Ophthalmology*, **2**, 449-468 and 506-516.

—— and HORRAX, G. (1919) Disturbances of spatial orientation and visual attention, with loss of stereoscopic vision. *Archives of Neurology and Psychiatry*, **1**, 385-407.

HUBEL, D. H. and WIESEL, T. N. (1970) Cells sensitive to binocular depth in area 18 of the *Macaque* monkey cortex. *Nature, London*, **225**, 41-42.

KLEIST, K. (1934) *Gehirnpathologie.* Leipzig: Barth.

KRAMER, F. (1970) Über eine partielle Störung der optischen Tiefenwahrnehmung. *Monatschrift für Psychologie und Neurologie*, **22**, 189-202.

LEHMANN, D. and WÄLCHLI, P. (1975) Depth perception and the location of brain lesions. *Journal of Neurology*, **209**, 157-164.

Martin, J. P. (1949) Consciousness and its disturbances. *Lancet*, **i**, 48–53.

Michel, F., Jeannerod, M. and Devic, M. (1965) Trouble de l'orientation visuelle dans les trois dimensions de l'espace. *Cortex*, **1**, 441–466.

Mitchell, D. E. and Baker, A. G. (1973) Stereoscopic after-effects: evidence for disparity-specific neurones in the human visual system. *Vision Research*, **13**, 2273–2288.

—— and Blakemore, C. (1970) Binocular depth perception and the corpus callosum. *Vision Research*, **10**, 49–54.

Neely, J. C. (1947) The treatment of traumatic diplopia. *British Journal of Ophthalmology*, **31**, 581–642.

Paterson, A. and Zangwill, O. L. (1944) Disorders of visual space perception associated with lesions of the right hemisphere. *Brain*, **67**, 331–358.

Pick, A. (1898) Ueber Störungen der Tiefenlocalisation in Folge cerebraler Herderkrankung. In: *Bieträge zur Pathologie und Pathologischen Anatomie des Centralnervensystems*. Berlin: Karger, Chapter 14.

Piéron, H. (1927) *Thought and the Brain*. London: Kegan Paul.

Poppelreuter, W. (1917/18) *Die psychischen Schädigungen durch Kopfschuss im Kriege 1914–1916*. Leipzig: Voss.

Richards, W. (1970) Stereopsis and stereoblindness. *Experimental Brain Research*, **10**, 380–388.

Riddoch, G. (1917) Dissociation of visual perceptions due to occipital injuries. *Brain*, **40**, 15–57.

—— (1935) Visual disorientation in homonymous half-fields. *Brain*, **58**, 376–382.

Rothstein, T. B. and Sacks, J. G. (1972) Defective stereopsis in lesions of the parietal lobe. *American Journal of Ophthalmology*, **73**, 281–284.

Sanderson, K. J., Darian-Smith, I. and Bishop, P. O (1969) Binocular corresponding receptive fields of single units in the cat dorsal lateral geniculate nucleus. *Vision Research*, **9**, 1297–1303.

Siegel, S. (1956) *Nonparametric Statistics for the Behavioural Sciences*. New York: McGraw-Hill.

Smith, S. and Holmes, G. (1916) A case of bilateral motor apraxia with disturbances of visual orientation. *British Medical Journal*, **1**, 437–441.

Stengel, E. (1944) Loss of spatial orientation, constructional apraxia and Gerstmann's syndrome. *Journal of Mental Science*, **90**, 753–760.

Symonds, C. P. (1945) Discussion on the ocular sequelae of head injuries. *Transactions of the Ophthalmological Societies of the United Kingdom*, **65**, 3–19.

Teuber, H. L., Battersby, W. and Bender, M. B. (1960) *Visual Field Defects after Penetrating Missile Wounds of the Brain*. Cambridge, Massachusetts: Harvard University Press.

Valkenburg, van C. T. (1908) Zur Kenntnis der gestörten Tiefenwhrnehmung. *Deutsche Zeitschrift fur Nervenheilkunde*, **34**, 322–337.

Wade, S. L. (1965) Loss of fusion following brain damage. *British Orthoptic Journal*, **22**, 81–83.

Yealland, L. R. (1916) Case of gunshot wound involving visual centre, with visual disorientation. *Proceedings of the Royal Society of Medicine*, **9**, 97–100.

Zangwill, O. L. (1951) Discussion on parietal lobe syndromes. *Proceedings of the Royal Society of Medicine*, **44**, 337–346.

(*Received August 2, 1977*)

Brain (1978), **101**, 591–606

A CLINICAL AND GENETIC STUDY OF SPINAL MUSCULAR ATROPHY OF ADULT ONSET

THE AUTOSOMAL RECESSIVE FORM AS A DISCRETE DISEASE ENTITY

by JOHN H. PEARN,[1] PETER HUDGSON *and* JOHN N. WALTON

(*From the Regional Neurological Centre, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, the Department of Neurology, the University of Newcastle upon Tyne, and the MRC Clinical Genetics Unit, Institute of Child Health, London*)

INTRODUCTION

THE nosology of the spinal muscular atrophies (SMA) has evoked considerable interest of late (Pearn, Carter and Wilson, 1973; Bundey and Lovelace, 1975; Emery, Davie, Holloway and Skinner, 1976*b*). It is now established that there is a severe and rapidly progressive form of onset in the first six months of life which is clinically and genetically distinct and leads to death before three years of age (Pearn *et al.*, 1973) and which is generally called Werdnig-Hoffmann disease or SMA Type 1. To date, there is no objective evidence to indicate unequivocal genetic heterogeneity in the late childhood and juvenile forms of the disease, often collectively called the Kugelberg-Welander syndrome (Gardner-Medwin, Hudgson and Walton, 1967; Pearn, 1974*a*; Bundey and Lovelace, 1975; Emery *et al.*, 1976*b*).

In all large series of cases of SMA reported in the past there have been occasional patients demonstrating adult onset of the disease (*see* Meadows, Marsden and Harriman, 1969; Namba, Aberfeld and Grob, 1970; Tsukagoshi, Shoji and Furukawa, 1970; Bundey and Lovelace, 1975; Emery, Hausmanowa-Petrusewicz, Davie, Holloway, Skinner and Borkowska, 1976*a*). Whether or not the varying clinical manifestations of the non-infantile forms imply that they represent a single disease with very variable clinical effects, or whether the adult-onset form is a separate entity, has not been formally established as yet, though Mapelli and Ramelli (1970) suggested that the adult variety is a separate disease. The question as to whether the Kugelberg-Welander syndrome in all its clinical presentations and SMA of adult onset represent variable clinical manifestations of a single disease entity, or whether they are different (but clinically overlapping) genetic entities is of considerable practical importance in relation to prognosis and genetic counselling, which are of especial importance in the management of an incurable and disabling group of conditions.

---

[1] Present address: Department of Child Health, Royal Children's Hospital, Brisbane, Queensland 4029, Australia.

Difficulties arising in clinical and genetic classification have been compounded by the inevitable bias in the selection of cases that tend to be referred to any one person or group (Emery *et al.*, 1976*b*). This difficulty has been resolved, in part, by a recent total population study of cases of SMA studied in North-east England, where all cases diagnosed as SMA occurring in a defined population of approximately two-and-a-half-million have been reliably identified. In this study (Pearn, 1974*b*) nine cases of the adult-onset form of the disease (occurring in six families) have been identified. An analysis of the genetic data derived from these patients and their families has given information on the nosology of the adult-onset variety of the disease which would have been unobtainable by other means.

The aims of the present study were: (a) to define the clinical features and criteria for classification of cases of SMA of adult onset which were not examples of SMA syndromes previously defined (dominantly inherited SMA of adult onset, distal SMA, sporadic adult motor neuron disease, neurogenic scapuloperoneal syndrome, etc.); and (b) to establish precise genetic data for the group (or groups) so defined.

METHODS

Ascertainment of Index Patients

All cases of SMA presenting to, or identified by, the clinical neurologists, neuropathologists and clinical electrophysiologists in the Regional Neurological Centre, Newcastle-upon-Tyne, over the ten-year period 1961-1970 were initially reviewed. Such is the nature of the clinical neurological practice and demography of the Region that such a search effectively led to a total population study of SMA in North-east England without evident bias in case selection (*see* Pearn, 1973).

Initially we included in the study all patients with evidence of progressive and diffuse denervation of skeletal muscles, in whom there was no clinical or electrophysiological evidence of sensory involvement. Provided that motor and sensory conduction velocity in several peripheral nerves was normal, convincing electromyographic evidence of progressive denervation was accepted as a criterion for initial inclusion of patients in the study, whether or not there was evidence of associated myopathic change. Serum creatine kinase (CK) activity was not used as a discriminant or diagnostic test, as it is well-known that the serum CK may be elevated in subacute or chronic forms of SMA (Hetnarska, Prot and Sawicka, 1968). Histological and histochemical preparations of muscle biopsy specimens were examined by one of us (P.H.) and while many of these showed evidence of secondary myopathic change, the nature of the primary denervating process was not in doubt. If the cerebrospinal fluid had been examined, and its protein content was elevated, the patient was excluded from the study.

After initial ascertainment, patients were excluded from the study on the basis of any one or more of the following criteria: (a) those with the clinical features of adult motor neuron disease; (b) those in whom a muscle biopsy showed neurogenic atrophy, but in whom either nerve conduction studies or CSF protein estimation had not been carried out; (c) those in whom the clinical course of the disease had not been progressive over a prolonged period—3 children with benign congenital hypotonia and 2 with poliomyelitis were thus excluded; (d) those with other well-defined disease processes of which muscular hypotonia and/or denervation may be a feature. These included patients with various lesions of the spinal cord, children with combined features of optic atrophy, anterior horn cell degeneration and mental retardation, and patients with cystinuria, the Prader-Willi syndrome and hypokalæmic periodic paralysis (on these criteria 30 cases were excluded, of which 17 were adults).

One-hundred-and-two patients with various clinical forms of SMA remained; families containing two affected children refused permission for further study and interview. After examination of hospital records, and clinical reassessment of surviving index patients, the following additional cases were excluded:

(a) those with an affected parent or child; in the absence of consanguinity, these were assumed to be examples of the dominant form of the disease (Zellweger, Simpson, McCormick and Ionasescu, 1972) This step, with a subsequent segregation analysis, in no way prejudged the issue of assessing the mode of inheritance in the remainder; families with an affected male relative, other than in the same sibship as the propositus, in which there was a possibility of X-linked recessive inheritance (Tsukagoshi, Shoji and Furukawa, 1970) were also excluded;

(b) infants with SMA Type I (Werdnig-Hoffmann disease), as defined by Pearn *et al.* (1973) and Pearn and Wilson (1973*a*);

(c) those with distal SMA (Dyck and Lambert, 1968; Meadows and Marsden, 1969*a*);

(d) those with the neurogenic scapuloperoneal syndrome (Meadows and Marsden, 1969*b*);

(e) those with other atypical clinical features. At first we excluded patients with a clinical picture indicative of muscular dystrophy of the X-linked Becker variety who showed marked hypertrophy of calf muscle but in whom there was evidence on investigation of SMA rather than of a primary myopathy, but on reflection we believe that these cases represent one form of clinical presentation of SMA.

Forty-eight index cases (42 children and 6 adults) with classical proximal progressive SMA were thus identified, and it is on this group that the genetic analyses were performed. In the 6 families containing cases of adult onset, there were 9 affected cases and the clinical features of the disease in these 9 patients will first be described before we give details of our genetic analyses.

THE CLINICAL FEATURES OF SMA OF ADULT ONSET

Of the 9 cases, 5 were male and 4 female and all were examined initially by one of us (J.N.W). They were subsequently assessed in detail by J.H.P. and all available sibs and first-degree relatives were also examined. A summary of the clinical details of the 9 adult-onset patients is given in Table 1.

Age at Clinical Onset

The age range at clinical onset in the 9 cases of adult onset was 15–50 years, with a median onset age of 35 years. The youngest case (a male with onset at 15 years) claimed sudden onset after a hand and arm injury in the factory where he worked, and at that stage some muscular weakness was apparent, but he was more severely affected on re-examination at the age of 19 years.

Age at Initial Medical Presentation

This forms a valuable reference point, and details can be checked for objectivity by reference to medical records in most cases. The age range encompassed at presentation was 15–50 years, with a median of 37 years. All the patients stated that they had had completely normal muscle strength in childhood, and up to the time of onset of initial symptoms. This antecedent history contrasts with the case histories of so many patients with the Kugelberg-Welander syndrome in whom,

TABLE 1. DIAGNOSTIC AND CLINICAL DETAILS OF 9 PATIENTS WITH SMA OF ADULT ONSET

Patient	*Sex*	*Age at clinical onset (years)*	*Age when first taken to doctor*	*Age at death or when last examined**	*Age at which appliances needed to assist walking*	*Unable to walk even with aids*	*Muscle biopsy or autopsy*	*EMG*	*Comments*
1 (B M)	F	30	34	63	60	—	N	NM	Patients 1 and 2 are sisters Marked intrafamilial concordance for clinical features of the disease.
2 (A M.)	F	40	46	57	—	—	N	—	—
3 (M R.)	F	50	50	63	58	—	NM	NM	Serum CK 26 5 IU/l ten years after diagnosis. Patients 3 and 4 were sibs Nerve conduction normal.
4 (W W.)	M	48	50	62*	56	58	—	—	Patient 4 not examined by J H.P , he was a coal-miner until 54 years of age.
5 (W S)	M	35	35	47	—	—	N	NM	Patients 5 and 6 were brothers. Good athlete in youth Serum CK of 1,050 IU/l ten years after initial diagnosis.
6 (L.S)	M	32	34*	42	—	—	—	—	Good athlete in youth Marked sib concordance for clinical features of the disease.
7 (E.S)	F	39	47	61	55	—	N	No abnormality detected	Serum CK 465 IU/l Gradual inexorable progression of weakness. Some asymmetry in early stages
8 (R.E)	M	32	35–40	70	50-60	—	N	N	—
9 (R I.)	M	15	15	29	29	—	N	N	Sudden onset after hand and arm injury, good athlete as a schoolboy

* = The patient had died — Indicates that either a muscle biopsy or EMG studies were not performed N = Findings on electromyography or muscle biopsy wholly indicative of denervation. NM = Findings on electromyography or muscle biopsy suggesting both denervation and myopathy but with predominant neuropathic features

in retrospect, it is usually noted by parents that the child always tended to have below average strength for his age. Indeed, in this adult-onset group 3 of the 5 males and one of the 4 females were exceptionally good athletes in their youth; another (Case 4, male) worked underground as a coalminer until the age of 54 years. The two affected brothers (Cases 5 and 6) completed normal military service during the Second World War. One of the two French cases described by Hurwitz, Lapresle and Garcin (1961) was also noted to be good at physical sport in her youth.

Onset of Disease

In 8 of the 9 cases the onset was insidious; awareness of weakness, or an appreciation of the significance of muscle fasciculations developed gradually. In retrospect, each of the 8 patients felt that the early features of the disease had been present for one or two years before real awareness dawned that something serious was wrong.

In only one case were early muscle cramps a feature, although most patients said that they functioned poorly in cold weather. In the description of these onset features, our experience exactly parallels that of Meadows, Marsden and Harriman (1969) although the familial patients with adult onset reported by these latter authors were dominantly inherited cases. The temporal range between the onset of initial symptoms (calculated in retrospect) and initial medical presentation was 0–8 years, with a median of 2 years.

Clinical Course

In comparison with the two forms of SMA of childhood onset (Pearn and Wilson, 1973*a*, *b*) the condition is relatively benign. All patients reported periods of apparent temporary arrest in the progression of muscle weakness. In our experience, however, the course is inexorably progressive although very slow, when reviewed in the long-term. Eventual confinement to a wheelchair is by no means inevitable in our experience (*see* Table 1). The rate of progression of the disease varies from family to family; no patient was able to walk completely unaided twenty years after the clinical onset of the disease. Muscle involvement is relatively symmetrical and becomes more so as the weakness progresses.

Life Expectancy

As 8 of the 9 patients were alive at the time of the study, it is not yet possible to prepare a life table for the disease. The patient who had died (Case 4, the coalminer) lived for fourteen years after the first clinical signs appeared, and his death was due to complications of occupational lung disease. The range of time-since-diagnosis in the survivors is eight to thirty-five years, with a median of thirteen years. The median age for all patients at the time of the study was sixty-one years. It can thus be seen that although this type of adult onset of SMA is an incapacitating disease, it is possible that life expectancy is not reduced.

NOSOLOGICAL AND GENETIC TECHNIQUES OF ANALYSIS OF DATA

Three basic techniques are available to resolve questions of genetic heterogeneity in clinical disease. These have been discussed in detail elsewhere (Pearn, 1974*a*). In summary they comprise:

(*a*) *Simple Intuitive Interpretation of Scattergram Clusters*

If familial cases of a disease can be assigned one or more quantitative indices for any manifestation of the illness (for example, age at clinical onset), then the construction of scattergrams may reveal obvious familial heterogeneity, and further formal statistical testing is not required. Cases of SMA within families were designated Sib 1, Sib 2 . . . etc; Carterian co-ordinates were constructed, and all familial sib-pairs were plotted. The technique has been used in other fields of biology (Gibbs and Brasier, 1971). If two familial diseases are present, the sib-pair points might be expected to show clustering.

(*b*) *Sib-sib Correlation Coefficients*

Haldane in 1941 suggested that if the correlation coefficient of sib-pair variables exceeded 0·5, then familial heterogeneity was present. This powerful tool has been used to resolve several recent neurological questions involving acute SMA Type I (Pearn, Carter and Wilson, 1973), Huntington's chorea (Brackenridge, 1972), and dystrophia myotonica (Bundey and Carter, 1972). In the current study, correlation coefficients were calculated for age at initial clinical onset, and for age at initial medical presentation, and the significance of differences from 0·5 (Null Hypothesis) were tested using Fisher's 'Z' transformation.

(*c*) *Frequency Distribution Curves*

Bimodality or polymodality in a histogram or frequency distribution curve suggests heterogeneity, provided that the series being tested is a consecutive unselected total population study. This simple technique convincingly demonstrates bimodality if subpopulations are present with their means widely separated in relation to their variances, and formal analysis is not required. If the means are not widely separated the statistical approaches to demonstrate bimodality of closely overlapping subgroups are notoriously difficult (Haldane, 1952).

Case Assessment

As stated above, many index patients of both adult-onset and juvenile cases of SMA as defined above were re-examined by one of us (J.H.P.) and a pedigree was constructed. Living first-degree relatives were also examined. For each case (both index and secondary cases) the age at clinical onset of the disease was assessed; in addition, the age at initial medical presentation was also documented—this had the advantage that it could be checked by documentary evidence.

RESULTS OF THE GENETIC ANALYSIS

Case finding details are shown in Table 2. There were 48 index patients and 17 secondary cases. Fig. 1 shows the scattergram, for age at clinical onset, obtained for the 21 sib-pairs involved (in only one family were there more than 2 affected

TABLE 2. CASE-FINDING DETAILS OF ALL PATIENTS WITH CHRONIC PROXIMAL SMA, NOT OF INFANTILE FORM

	Familial cases				*Combined cases*			
	Families	*Index patients*	*Secondary cases*	*Sporadic cases (Index pts=No. of families)*	*Families*	*Index patients*	*Secondary cases*	*Total*
Children	17	19	14	23	40	42	14	56
Adults	3	3	3	3	6	6	3	9
Total	20	22	17	26	46	48	17	65

sibs). It can be seen clearly, by inspection, that a discrete familial form of the disease exists, showing an adult onset of symptoms. An almost identical pattern is obtained by plotting the 'age at initial medical presentation' data.

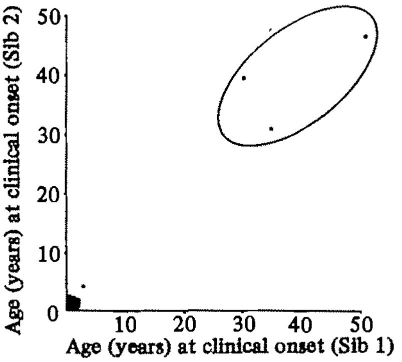


FIG. 1. Scattergram for age at clinical onset of 21 sib-pairs with non-infantile SMA. Each point represents a family in which two (or more) cases of SMA have occurred.

Table 3 shows the correlation coefficients for the sib-pair data. It can be seen that the very high correlation coefficients observed (0·90 for both raw and log data) for both age-at-onset and age-at-presentation, indicate genetic heterogeneity. In this series of cases, it can be further shown that this heterogeneity is due solely to the inclusion of the adult group (Table 3). After the removal of the 9 adult-onset cases, the correlation coefficient falls and does not differ significantly from 0·5 (even for the raw data with a correlation coefficient of 0·78, 95 per cent. confidence limits are 0·49–0·91). This result implies, incidentally, that it is unlikely that there is further genetic heterogeneity (with respect to age at onset) in the juvenile-onset group.

TABLE 3. CORRELATION COEFFICIENTS FOR SIB-PAIR CORRELATES. DATA FROM 20 FAMILIES AND 22 INDEX PATIENTS

		Correlation	*Coefficients*
	*Type of data**	*Age at clinical onset*	*Age at initial medical presentation*
All cases of non-infantile SMA (adult and juvenile)	Raw data	0·98	0·98
	Log data	0·91	0·90
Juvenile-onset cases only	Raw data	0·78	0·46
	Log data	0·56	0·55

* The conversion of raw data to log data ensured a Normal distribution.

TABLE 4. GENETIC DETAILS OF 9 CASES OF SMA OF ADULT ONSET; INCLUDES TRACING SOURCE, BIRTH RANK, TYPE OF ASCERTAINMENT (INDEX *vs.* SECONDARY CASE), AND FAMILY DATA

			Children of index cases		*Cousins children of*					*Ancestry grandparents' birthplace*				
					Father's		*Mother's*		*Social*	*Father's*		*Mother's*		
Kindred	*Source†*	*Affected sibship‡*	*Males*	*Females*	*Brothers*	*Sisters*	*Brothers*	*Sisters*	*class§*	*Father*	*Mother*	*Father*	*Mother*	*Comments*
1	NR 33887	M–/06, F–/08, *_F1/10_, F–/12, M–/14, F–/14, F–/16, _F–/16_, F–/18, M–/20, M–/22	1	1	10	3	10	6	1	Poland	Poland	Russia	Russia	F–/16 and _F–/16_ are fraternal twins. _See_ fig 3 Two sisters, F–/08 and F–/14 have diabetes mellitus, but no neuromuscular abnormality Marked intrafamilial concordance for clinical features of SMA. _F–/16_ also has 2 children (both daughters, normal).
2	NR 17549	F–/?08, _M–/?10_, *_F12/12_	1	1	2	9	1	8	5	Durham	Durham	Durham	Durham	_M–/?10_ not re-examined personally (died), but reliable information obtained
3	NR 22991	F–/20, M–/22, *_M2/26_, M–/29, _M–/31_	2	2	2	9	1	8	2	Durham	Durham	Durham	Durham	No isonymy in ancestral kindred. Striking intrafamilial concordance
4	NR 34661	F–/?09, *_F8/12_	0	0	0	0	3	7	5	Staffs	Staffs	Durham	Durham	—
5	NR 46247	F–/–, F–/–, *_M2/07_	0	0	NK	NK	NK	NK	4	'England'	'England'	'England'	'England'	—
6	NX 54000	*_M2/47_, M–/49, M–/52	1	1	5	5	3	6	4	Norfolk	Norfolk	Durham	Durham	—

* Index case † Tracing source NR = Case traced from Regional Neurological Centre, Newcastle upon Tyne, NX = Case traced from Records of Newcastle General Hospital. ‡ Birth month and year, italic denotes an affected case. § Classification of General Register Office (1966) NK = Details unknown

Fig. 2 is the frequency distribution histogram for age-at-onset and age-at-presentation for all cases, both familial and simplex, in this total population study. The simplest interpretation of these figures is that there are two non-overlapping populations present, and that one of these is a separate familial entity of an adult-onset disease.

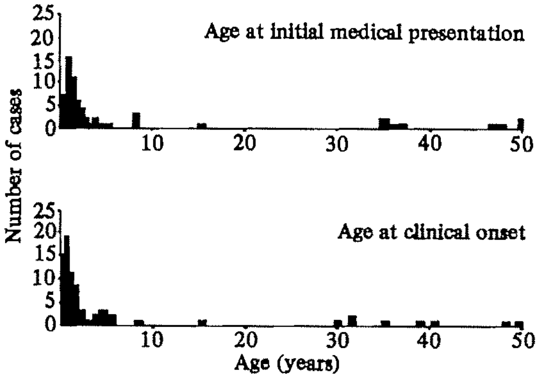


FIG. 2 Frequency distribution histogram for age-at-onset, and age-at-presentation, of 65 consecutive cases of non-infantile SMA

It is thus possible, using these three criteria, to define the clinical syndrome of SMA of adult-onset as one with onset not before 15 years of age, and usually several years later; defined in this way, the 9 cases of adult onset were considered as a separate group, and further genetic studies were undertaken upon them. Genetic data are given in Table 4.

The sex ratio in the adult cases was 5:4 (males:females). Segregation ratios are shown in Table 5. Because of the complexity of the interpretation of segregation ratios dependent on the type of ascertainment (in this case by multiple incomplete selection, *see* Crow, 1965), the calculation of the appropriate error formula is difficult. If one uses only those sibs born after the index patients, a more simple formula can be used, and the observed segregation ratio of 0·20 has 95 per cent confidence limits of 0–0·40. Although this observed value does not differ significantly from 0·25 (the Null Hypothesis for autosomal recessive inheritance),

TABLE 5. SEGREGATION ANALYSIS OF ALL SMA CASES WITH ADULT ONSET (BOTH FAMILIAL AND NON-FAMILIAL)

Group	*Clinically normal*		*Affected with SMA*		*Segregation ratio*	*Standard error*	*95 per cent confidence limits*
	Males	*Females*	*Males*	*Females*			
All sibs of index patients	8	10	2	1	0·14	0·076	0–0·29
All sibs born after index patients	6	6	2	1	0·20	0·103	0–0·40

two interpretations remain possible. One is that all cases of the syndrome are the result of autosomal recessive inheritance, but that all sibs have not yet passed through their risk period. A study of the families shows this to be the most likely possibility. A second possibility is that a small percentage of all simplex families (containing isolated cases) are examples of a new dominant mutation occurring in the index case. For genetic counselling purposes, this percentage is unlikely to be greater than 10 per cent as a current working hypothesis. The 9 adult patients in this study had a total of 10 children, all of whom were normal at the time of examination, the youngest was 15 years of age and the remaining 9 were all over 30 years of age. A typical family (Family 1 in Table 4) is shown in Fig. 3.

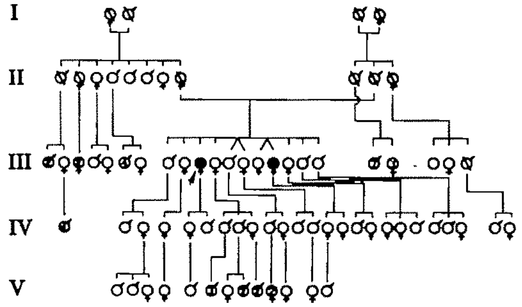


FIG. 3. Family tree of Family 1 in Table 4. A typical family in which is occurring SMA of adult onset, due to an autosomal recessive gene. Roman numerals indicate generations; the arrow indicates the index case

The prevalence of the disease and estimates of gene frequency have been assessed by reference to corrected population figures from the Registrar General (1972), to the Registrar General's Abridged Life Tables for 1965 (the mid-point of the survey dates), and to unpublished data provided by the 10 Medical Officers of Health responsible for the population studied.

Eight of the patients were alive on June 30, 1971 (5 familial and 3 simplex cases) in an estimated population of 2,488,000, giving a prevalence figure of 0·32 per 100,000 of the general population. Birth incidence was calculated as 1 in 343,000 live births. Assuming that all cases are due to autosomal recessive genes, the carrier frequency is 1 in 290 persons, and the corresponding gene frequency $q = 0{\cdot}00171$. If one assumes that 10 per cent of index cases are the result of new dominant mutations, the corresponding gene frequency (q) is 0·00161 (carrier frequency of 1 in 308). A working estimate for the carrier (heterozygote) frequency is thus 1 in 300 in the general population.

DISCUSSION

Differential diagnosis in this condition is a two-step process. A conclusive diagnosis of SMA requires muscle biopsy with histochemical study, electrophysiological studies to establish normality of motor and sensory nerve conduction velocity and usually examination of CSF to show that its protein content is normal, since a subacute, predominantly motor, proximal motor neuropathy can mimic the condition. The electrophysiological studies should be repeated later in order to exclude mixed peripheral neuropathies with relatively late involvement of sensory fibres, such as that which may occur up to five years after clinical presentation in cases of peroneal muscular atrophy, in which condition, however, muscular atrophy and weakness are predominantly distal (Gilliatt, 1959; Buchthal and Behse, 1977). As in some cases of motor neuron disease, serum creatine kinase (CK) activity is often elevated in SMA of adult onset (*see also* Hetnarska, Prot and Sawicka, 1968) usually in the non-specific range; in our experience, in spite of secondary myopathic change which commonly develops in affected muscles, one seldom encounters levels of CK activity such as those seen in the primary myopathic disorders.

A difficult problem, at the time of initial presentation, is differentiation of this disease from familial motor neuron disease (Amick, Nelson and Zellweger, 1971), especially the autosomal recessive form of motor neuron disease in its very early stages (Dumon, Macken and deBarsy, 1971). However, the rapid progression, asymmetry, appearance of upper motor neuron signs and early appearance of bulbar signs in the latter condition should resolve diagnostic difficulties within months of the initial presentation. There is one reported type of familial motor neuron disease, however, with longer survival and probable recessive inheritance (*see* Pedigree 14 of Horton, Eldridge and Brody, 1976) whose relationship to recessive SMA of adult onset remains to be determined.

The second step in differential diagnosis involves the determination of the genetic type of SMA which is present. It is probable, but as yet unconfirmed, that the three genetic types of the disease have varying clinical features; the clinical spectrum of the X-linked recessive and autosomal dominant forms (Emery, 1971) have yet to be accurately defined. If the parents are known to be unaffected and if the patient is a female, it is likely that the condition is due to an autosomal recessive gene. If the patient is a male, it is important to examine male relatives in the mother's family, as a small (but unknown) percentage of such cases are due to X-linked recessive genes. Of familial cases of SMA of adult onset, the proportion of dominant to recessive causal genes is approximately 2:1 (Pearn, 1974*b*); of the 9 adult-onset cases of Meadows *et al.* (1969), 2 were familial, both dominant.

Management follows the pattern of all clinically-similar progressive neuromuscular diseases; in this case tempered by honest reassurance that life is not likely to be shortened. Regular physiotherapy with emphasis on hydrotherapy, occupational therapy with modification of the domestic environment, and genetic counselling as described below form the mainstays of management.

Genetic counselling of patients with SMA of adult onset is relatively straightforward. The risk to sibs is approximately 1 in 5 in sporadic cases, and 1 in 4 in familial cases. The estimated risk to children of affected individuals is low, and is no greater than 1 in 20, in our present state of knowledge of the disease. In unequivocal recessive cases the risk is 1 in 600 (1 × 1/300 × 1/2). Provided that sibs of index cases are demonstrably normal after full neurological examination, the risk to nephews and nieces of index cases is low, if there is no consanguinity. It may be appropriate to examine electromyographically clinically normal individuals within affected families, if genetic advice is sought.

A refinement in genetic counselling of clinically normal subjects would take into account the extent to which the risk period has passed. Because of the paucity of published cases, it is not yet possible to construct a cumulative frequency distribution curve for age at clinical onset, but a provisional 50 per cent point of 35 years can be used. For example, the sibs of a simplex patient have a risk of only 1 in 10 (1/2 × 1/5) of developing the disease if they are normal at 35 years of age. In familial cases, the striking concordance (both in age at onset, and in clinical progression) that we and others have observed will enable counselling to be given with greater confidence, especially in the case of a normal subject who is well past the age of onset manifested by affected sibs.

A surprising finding in this study has been the absence of consanguinity in the case of such a relatively rare gene; consanguinity has not been reported either in other reports of families containing cases of this condition (*see* Meadows *et al.*, 1969). One would expect, on average, to encounter between 10–15 per cent of consanguineous marriages among the parents of index cases (Maynard-Smith, Penrose and Smith, 1961), assuming a general population consanguinity rate of between 0·5 and 0·1 per cent. The absence of consanguinity in reported families may be due to chance, or it may be due to the fact that index patients tend to be older when questioned about details of their families (the median age in this study was 60 years); in these circumstances interparental relationships, if any, are difficult to retrieve. The low consanguinity observed suggests that the recessive genes involved are allelic.

There are at least three separate genes which can cause SMA of adult onset (Table 6). It is not yet possible to define different clinical features for these conditions, but there is a suggestion that the dominant form of the disease is clinically milder, of slower progression (Case 3 of Kugelberg and Welander, 1956; Emery,

TABLE 6. SUMMARY OF REPORTED FAMILIAL CASES OF CHRONIC PROGRESSIVE PROXIMAL SMA OF ADULT ONSET

	Authors	*No. of families*	*Median age of onset (yrs)*
SMA of adult onset (autosomal recessive)	Meadows *et al.*, 1969 (Case 13)	1	40–50
	Present series	3	37
SMA of adult onset (autosomal dominant)	Meadows *et al.*, 1969 (Case 14)	1	25–50
SMA of adult onset (X-linked recessive)	Tsukagoshi *et al.*, 1970	1	21

1971; Pearn, 1974*b*), and may be of earlier onset. In common with all types of dominantly-determined disease, wide intrafamilial variation occurs within families. The X-linked recessive form of the disease may also be generally of earlier onset. It is interesting to note that the sporadic male cases which have been reported, and which could have been due either to autosomal or X-linked recessive genes, tend to be of earlier onset (*see* Cases 1 and 2 of Gross, 1966; Case 18 of Peters, Opitz, Goto and Reese, 1968; and Family 6 in the current series). It has further been suggested that there are two genetic forms of the adult-onset X-linked form of the disease (Emery, 1971). Many familial cases in the literature cannot be classified genetically because only males were affected, and only a single sibship is involved (*see* Cases 1, 2 and 3 of Tsukagoshi *et al.*, 1965). It is hoped that as more familial cases are reported, a more complete picture will emerge.

SUMMARY

A clinical and genetic study of spinal muscular atrophy (SMA) of adult onset is reported. A genetic analysis of all cases of SMA occurring over a ten-year period in North-east England (48 index cases) has shown that chronic proximal SMA of adult onset is a distinct clinical and genetic entity, and is not a variant of the more common and relatively benign late juvenile cases. Nine cases of SMA of adult onset have been studied, occurring in 6 families. The median age of clinical onset was 35 years and the mean age at initial medical presentation was 37 years. The sex ratio was 5:4 (males:females). The condition is relatively benign and there is no evidence to date that life expectancy is shortened; there is usually no premonitory evidence of muscular weakness in early adult life. The muscular involvement is relatively symmetrical and the distal musculature is well preserved; clinical progression of the disease is interrupted by periods of apparent arrest. No patient was able to walk completely unaided twenty years after the initial clinical onset; the median age of patients in the study was 61 years but only one was confined to a wheelchair. In the early stages the recessive form of familial motor neuron disease must be excluded. A segregation analysis of sibs born after index cases was undertaken (segregation ratio of 0·20). This finding is consistent with autosomal recessive inheritance with an extended period during which the disease might initially present. The presence of new dominant mutations cannot be excluded, but is unlikely to account for more than 10 per cent of cases. The carrier rate in the English population is estimated to be 1 in 300, with a gene frequency $q = 0{\cdot}00165$. Prevalence is 0·32 per 100,000 in the general population. Empirical risks for genetic counselling are presented.

ACKNOWLEDGEMENTS

J.H.P. wishes to thank Professor C. O. Carter for continuing counsel and advice, and we are grateful to Dr. J. B. Foster and Dr. D. Gardner-Medwin of the Regional Neurological Centre, Newcastle-upon-Tyne, for permission to include their patients in this study. This study was aided by grants from the Medical Research Council and from the Muscular Dystrophy Group of Great Britain.

REFERENCES

AMICK, L. D., NELSON, J. W. and ZELLWEGER, H. (1971) Familial motor neuron disease, non-Chamorro type: report of kinship. *Acta Neurologica Scandinavica*, **47**, 341-349.

BRACKENRIDGE, C. J. (1972) Familial correlations for age at onset and age at death in Huntington's disease. *Journal of Medical Genetics*, **9**, 23-32.

BUCHTHAL, F. and BEHSE, F. (1977) Peroneal muscular atrophy (PMA) and related disorders. I. Clinical manifestations as related to biopsy findings, nerve conduction and electromyography. *Brain*, **100**, 41-66.

BUNDEY, S. and CARTER, C. O. (1972) Genetic heterogeneity for dystrophia myotonica. *Journal of Medical Genetics*, **9**, 311-315.

—— and LOVELACE, R. E. (1975) A clinical and genetic study of chronic proximal spinal muscular atrophy. *Brain*, **98**, 455-472.

CROW, J. F. (1965) Problems of ascertainment in the analysis of family data. In: *Genetics and the Epidemiology of Chronic Diseases*. Edited by M. W. Shaw and W. J. Schull. Washington: U.S. Dept. Health, Education and Welfare, pp. 23-44.

DUMON, J., MACKEN, J. and DEBARSY, Th. (1971) Concordance for amyotrophic lateral sclerosis in a pair of dizygous twins of consanguineous parents. *Journal of Medical Genetics*, **8**, 113-116.

DYCK, P. J. and LAMBERT, E. H. (1968) Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. II. Neurologic, genetic and electrophysiologic findings in various neuronal degenerations. *Archives of Neurology, Chicago*, **18**, 619-625.

EMERY, A. E. H. (1971) The nosology of the spinal muscular atrophies. *Journal of Medical Genetics*, **8**, 481-495.

—— HAUSMANOWA-PETRUSEWICZ, I., DAVIE, A. M., HOLLOWAY, S., SKINNER, R. and BORKOWSKA, J. (1976*a*) International collaborative study of the spinal muscular atrophies. Part 1: Analysis of clinical and laboratory data. *Journal of the Neurological Sciences*, **29**, 83-94.

—— DAVIE, A. M., HOLLOWAY, S. and SKINNER, R. (1976*b*) International collaborative study of the spinal muscular atrophies. Part 2: Analysis of genetic data. *Journal of the Neurological Sciences*, **30**, 375-384.

GARDNER-MEDWIN, D., HUDGSON, P. and WALTON, J. N. (1967) Benign spinal muscular atrophy arising in childhood and adolescence. *Journal of the Neurological Sciences*, **5**, 121-158.

GENERAL REGISTER OFFICE (1966) *Census 1961. England and Wales. Occupational Tables.* London: H.M.S.O. Table 20, p. 125.

GIBBS, J. N. and BRASIER, C. M. (1971) Correlation between cultural characters and pathogenicity in Ceratocystis ulmi from Britain, Europe and America. *Nature, London*, **241**, 381-383.

GILLIATT, R. W. (1959) Peripheral nerve conduction in neurological patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **22**, 344.

GROSS, M. (1966) Proximal spinal muscular atrophy. *Journal of Neurology, Neurosurgery and Psychiatry*, **29**, 29-34.

HALDANE, J. B. S. (1941) The relative importance of principal and modifying genes in determining some human diseases. *Journal of Genetics*, **41**, 149-157.

—— (1952) Simple tests for bimodality and bitangentiality. *Annals of Eugenics, London*, **16**, 359-364.

HETNARSKA, L., PROT, J. and SAWICKA, E. (1968) Creatine phosphokinase activity in spinal muscular atrophy. *Journal of the Neurological Sciences*, **6**, 261-267.

HORTON, W. A., ELDRIDGE, R. and BRODY, J. A. (1976) Familial motor neuron disease. Evidence for at least three different types. *Neurology, Minneapolis*, **26**, 460-465.

HURWITZ, L., LAPRESLE, J. and GARCIN, R. (1961) Atrophie musculaire neurogène de topographie proximale et symétrique simulant une myopathie: étude de deux observations. *Revues Neurologiques*, **104**, 97-107.

KUGELBERG, E. and WELANDER, L. (1956) Heredofamilial juvenile muscular atrophy simulating muscular dystrophy. *Archives of Neurology and Psychiatry*, **75**, 500-509.

MAPELLI, C. and RAMELLI, E. (1970) Familial progressive spinal amyotrophy with limb root distribution and onset in adult life (neurogenic pseudomyopathy of Wohlfart-Kugelberg-Welander). In: *Muscle Diseases*, International Congress Series No. 199. Edited by J. N. Walton, N. Canal and G. Scarlato. Amsterdam: Excerpta Medica, pp. 551-554.

MAYNARD-SMITH, S., PENROSE, L. S. and SMITH, C. A. B. (1961) *Mathematical Tables for Research Workers in Human Genetics*. London: Churchill, Table 18, p. 26.

MEADOWS, J. C. and MARSDEN, C. D. (1969*a*) A distal form of chronic spinal muscular atrophy. *Neurology, Minneapolis*, **19**, 53-58.

—— —— (1969*b*) Scapuloperoneal amyotrophy. *Archives of Neurology, Chicago*, **20**, 9-12.

—— —— and HARRIMAN, D. G. F. (1969) Chronic spinal muscular atrophy in adults. Part 1: The Kugelberg-Welander syndrome. *Journal of the Neurological Sciences*, **9**, 527-550.

NAMBA, T., ABERFELD, D. C. and GROB, D. (1970) Chronic proximal spinal muscular atrophy. *Journal of the Neurological Sciences*, **11**, 401-423.

PEARN, J. H. (1973) The gene frequency of acute Werdnig-Hoffmann disease (SMA Type I). A total population survey in North-East England. *Journal of Medical Genetics*, **10**, 260-265.

—— (1974*a*) The Spinal Muscular Atrophies of Childhood. A Genetic and Clinical Study. Ph.D. Thesis, University of London, pp. 96-109.

—— (1974*b*) The Spinal Muscular Atrophies of Childhood. A Genetic and Clinical Study. Ph.D. Thesis, University of London, pp. 160-171.

—— CARTER, C. O. and WILSON, J. (1973) The genetic identity of acute infantile spinal muscular atrophy. *Brain*, **96**, 463-470.

PEARN, J. H. and WILSON, J. (1973*a*) Acute Werdnig-Hoffmann disease. Acute infantile spinal muscular atrophy. *Archives of Diseases of Childhood*, **48**, 425–430.

—— —— (1973*b*) Chronic generalized spinal muscular atrophy of infancy and childhood. Arrested Werdnig-Hoffmann disease. *Archives of Diseases of Childhood*, **48**, 768–774.

PETERS, H. A., OPITZ, J. M., GOTO, I. and REESE, H. H. (1968) The benign proximal spinal progressive muscular atrophies. A clinical and genetical study. *Acta Neurologica Scandinavica*, **44**, 542–560.

REGISTRAR GENERAL (1965) *Statistical Review of England and Wales for the Year 1965*. Part I. London: H.M.S.O. Appendix B, Abridged Life Table 1965, p. 412.

—— (1972) *Statistical Review of England and Wales for the Year 1970*. Part I. London: H.M.S.O.

TSUKAGOSHI, H., NAKANISHI, L., KONDO, K. and TSUBAKI, T. (1965) Hereditary proximal neurogenic muscular atrophy in adult. *Archives of Neurology, Chicago*, **12**, 597–603.

—— SHOJI, H. and FURUKAWA, T. (1970) Proximal neurogenic muscular atrophy in adolescence and adulthood with X-linked recessive inheritance. *Neurology, Minneapolis*, **20**, 1188–1193.

ZELLWEGER, H., SIMPSON, J., McCORMICK, W. F. and IONASESCU, V. (1972) Spinal muscular atrophy with autosomal dominant inheritance. *Neurology, Minneapolis*, **22**, 957–963.

(*Received January 19, 1978*)

Brain (1978), **101**, 607–633

THE ROLE OF FRONTAL AND PARIETAL CORTEX IN COGNITIVE PROCESSING

TESTS OF SPATIAL AND SEQUENCE FUNCTIONS

by BETTY ANN BRODY[1] *and* KARL H. PRIBRAM[2]

(*From the Department of Psychology, Stanford University, Stanford, California 94305*)

INTRODUCTION

SINCE Jacobsen first demonstrated that monkeys with resections of the anterior frontal cortex are unable to learn delayed-response or spatial delayed-alternation tasks (Jacobsen, 1936; Jacobsen and Nissen, 1937), there have been many attempts to interpret these findings in order to formulate a mechanism for frontal cortical control of complex behaviour. Recent interpretations have emphasized the fact that these tasks involve right-left discriminations and therefore might tap spatial memory (Goldman and Rosvold, 1970; Goldman, Rosvold, Vest and Galkin, 1971).

Although spatial cognitive processes have classically been attributed to the domain of the posterior parietal cortex in humans (Critchley, 1953), several studies in the clinical literature have also noted certain types of spatial impairments following frontal cortical damage. These studies have provided suggestive evidence for a dichotomy between the nature of the spatial impairments produced by damage to the frontal and parietal cortex. Patients with parietal cortical damage were found to have difficulty in setting a line to vertical against a conflicting background (Teuber and Mishkin, 1954) and to be unable to make conceptual spatial rotations of maps (Semmes, Weinstein, Ghent and Teuber, 1963) or visual patterns (Butters and Barton, 1970; Butters, Barton and Brody, 1970); in contrast patients with frontal damage had no such difficulty. Conversely, patients with frontal cortical damage were found to have difficulty in setting a line to vertical when their own bodies were tilted with respect to vertical (Teuber and Mishkin, 1954), pointing to the parts of their own body corresponding to those designated on a diagram (Semmes *et al.*, 1963), or making a series of right-left discriminations with respect to varying orientations on a map different from the orientation of their own bodies (Butters, Soeldner and Fedio, 1972). Patients with parietal damage also had difficulty with some of these latter tasks; however, if the parietal damage was confined to the right hemisphere, the patients were unimpaired. On the basis of their findings Teuber and his colleagues (Semmes *et al.*, 1963; Teuber, 1964) characterized the general impairment following parietal damage as one involving extrapersonal spatial orientation, that is, a difficulty with discriminations involving the spatial relationships among external stimuli. In contrast, they characterized the impairment following frontal cortical damage as one involving personal spatial orientation, that is, a difficulty with discriminations dependent on the accurate assessment of the body's orientation in space.

---

[1] Present address: University of Pennsylvania, School of Medicine, Box 192, Philadelphia, Pennsylvania 19174.

[2] Requests for reprints may be sent to Karl H. Pribram, Department of Psychology, Stanford University, Stanford, California 94305.

In order to specify the locus of the deficit more accurately and to correlate these clinical findings with the vast amount of information obtained from research with nonhuman primates, Pohl (1973) attempted to test the dichotomy between personal and extrapersonal spatial orientation using monkeys with dorsolateral frontal or with posterior parietal ablations. Since it had been assumed that the salient feature of the tasks defined as measures of personal spatial orientation was the necessity of making right-left discriminations, Pohl used the place reversal task (go left to a criterion—go right to a criterion) as the measure of personal spatial orientation. For comparison he used a landmark discrimination (go to the foodwell nearer the landmark) and a landmark discrimination reversal task (go near the landmark to a criterion—go far from the landmark to a criterion) as measures of extrapersonal spatial orientation. The solutions for these latter spatial tasks were based on the spatial location of an external referent, the landmark. The monkeys with frontal lesions were impaired on the place reversal but not the landmark reversal while the opposite was true for the monkeys with parietal lesions. Pohl interpreted his results to indicate that the personal-extrapersonal dichtomy is appropriate for monkeys as well as humans.

Despite the fact that both patients and monkeys with frontal damage demonstrate significant impairments on certain tasks involving right-left discriminations, there remains some difficulty with emphasizing right-left disorientation or the more general concept of personal spatial disorientation as the primary basis of the syndrome following frontal damage. First, the clinical literature indicates that right-left disorientation classically follows parietal cortical damage (Gerstmann, 1940; Critchley, 1953) rather than frontal damage. Secondly, the most striking effect of frontal cortical damage in patients is their tendency to perseverate previous responses; aspects of this syndrome have been tested empirically with card sorting (Milner, 1963), a multiple object search task (Poppen, Pribram and Robinson, 1965), and multistep instructions (Luria, Pribram and Homskaya, 1964; Luria, 1966). An emphasis on personal spatial disorientation cannot account for these findings. Thirdly, the experimental data obtained on monkeys indicate that if lesions are confined to the focus within dorsolateral frontal cortex attributed to be selectively involved with spatial function, a right-left discrimination requirement is not sufficient by itself to produce the deficit; memory must be taxed, either with imposed delays or with alternations or reversals of response requirements (Goldman and Rosvold, 1970; Goldman *et al.*, 1971).

By contrast to these theories involving spatial functions, some time ago Pribram (1958, 1961) pointed out that the delayed-response and delayed-alternation tasks require the sequencing of behaviours. He and his co-workers suggested that the function of the anterior frontal cortex is to provide a working memory in which these sequences can be flexibly ordered (Pribram, Ahumada, Hartog and Ross, 1964). The clinical literature also provides evidence that patients with frontal damage have considerable difficulty with the temporal organization of behaviour, particularly when flexibility is required. The almost pathognomonic tendency of such patients to perseverate portions of instructions occurs most notably when they attempt to perform a sequence of different behaviours (Luria *et al.*, 1964; Milner, 1964; Luria, 1966). Moreover, the difficulty similar patients have shown in identification of body parts (Semmes *et al.*, 1963), in a stylus maze task (Milner, 1964), or in a path reading task (Butters *et al.*, 1972) has been attributed to a deficit in personal spatial orientation, but the conflicting sequential response requirements are equally critical features of these tasks (Semmes *et al.*, 1963; Milner, 1971). Milner (1971) has reported that her patients with frontal damage could recognize previously-seen items but could not recall in what order they had been seen, suggesting ineffective 'temporal tagging' of information.

Pribram had earlier suggested that the difficulty monkeys with frontal resections have with sequencing tasks such as delayed alternation might be due to an inability to parse stimuli into useful patterns. He and his students were able to improve the performance of such monkeys on delayed alternation by the simple expedient of imposing a temporal pattern to the stimuli (Pribram and Tubbs, 1967; Pribram, Plotkin, Anderson and Leong, 1977). Also in Pribram's laboratory, Pinto-Hamuy and Linck (1965) directly examined the role of the frontal cortex in sequencing by teaching monkeys to press different stimulus-response panels in a particular sequential order. On the basis of earlier work by Kimble and Pribram (1963) they investigated the possibility that sequences organized by external cues and those depending on internal cues would be differentially influenced by frontal resections. They found that if the sequential order was externally imposed such that the monkeys were always required to choose the same unique sequence, those monkeys with frontal ablations were able to learn the problems at a normal rate. On the other hand, if the only rule imposed was that a sequence on any one trial must contain no repetitions, the monkeys with frontal ablations demonstrated a deficit. These authors suggested that during the latter type of sequence the monkey must internally organize the sequence within each trial by maintaining a memory of each prior press; whereas, during the externally-ordered sequence the external visual cues contained the information needed to order the responses. They concluded therefore that the frontal cortex is necessary to order sequential behaviours whenever such sequences require organization within memory.

However, another difference between the two types of sequences might have been an important variable in the study by Pinto-Hamuy and Linck. The stimuli were presented on a four-by-four stimulus-panel array such that the locations of the stimuli changed only between trials. The internally-ordered sequence could correctly be completed by simply pressing each panel once, remembering only the location of the previous press. In fact, one of the internally-ordered sequences (red, red, red) required such a spatial solution. By contrast, in the externally-ordered sequences the pattern as well as the location of the cued panel could be used to solve the problem. The deficit on the internally-ordered sequence is equally well interpreted in terms of the hypothesis that following frontal resection monkeys have a deficit in spatial memory.

An experimental analysis of both the spatial and the temporal theories was therefore undertaken and is reported here in two studies. The first of the studies attempts to clarify the relevance of a personal-extrapersonal spatial dichotomy to frontal and parietal cortical function. Monkeys with bilateral anterior frontal or with bilateral posterior parietal ablations were trained on variations of a spatial task designed to test the dichotomy as simply as possible while avoiding the use of either right-left discriminations or reversal problems. As a test of personal spatial orientation the monkey was required to press the panel next to a panel he had previously selected. As a test of extrapersonal spatial orientation the monkey was required to press the panel next to a green panel. The personal-extrapersonal spatial theory would clearly predict a double dissociation of function on these two tasks.

The purpose of the second study was to determine if monkeys with frontal ablations have deficits which are related to an inability to organize sequences independent of a spatial component and to examine the monkeys' dependence on external cues in learning such sequences. Monkeys with anterior frontal or with posterior parietal ablations were tested on sequence problems whose solutions were completely independent of the spatial locations of the stimuli. We expected that monkeys with frontal resections would show a greater deficit on internally-ordered sequences than on externally-ordered sequences. In contrast, we expected those with parietal resections to show a completely normal performance under both conditions.

METHODS

Subjects

Fourteen juvenile rhesus monkeys (*Macaca mulatta*) served as subjects; their range of weight at operation was 2·8 to 3·6 kg. Three of these remained as normal controls (Normal Group), 4 sustained bilateral posterior parietal lesions (Parietal Group), and 7 (of which only 4 were used in the spatial tasks) sustained bilateral anterior frontal lesions (Frontal Group).

Surgery and Histology

Prior to surgery all monkeys were tranquillized with Ketamine (11 mg/kg i.m.) and then anæsthetized with intravenous sodium pentobarbital until eyelid reflexes were absent. A saline drip through an intravenous catheter was maintained throughout surgery during which additional doses of pentobarbital were administered as required. All ablations were performed as a one-stage bilateral aseptic procedure. The cortex was exposed with a full calvarium flap which crossed the midline and was hinged on one set of temporal muscles. Cortical gray matter was removed bilaterally by subpial aspiration using a 19-gauge Pribram Sucker designed to avoid damage to underlying white matter. Bleeding was controlled by gentle packing with cottonoid patties or, rarely, electrocauterization. The dura was closed with individual silk sutures; and muscle, subcutaneous tissues, and skin were closed in layers. Following surgery, long-acting bicillin (300,000 U i.m.) was routinely administered to all of the monkeys, and dexamethasone (2 mg i.m.) was also given to those sustaining frontal ablations.

The anterior frontal lesion was defined by von Bonin and Bailey's (1947) areas FD, FDΔ, and FDγ, extending from the midline to the lip of the lateral surface through both banks of the sulcus principalis, and from the depth of the anterior bank of the arcuate sulcus rostrally to include the entire frontal pole.

The posterior parietal lesion was defined by von Bonin and Bailey's areas PF, PC, PE, and the more dorsal portions of areas OA and TA on the lateral surface. The lesion included the anterior bank of the lunate sulcus and extended rostrally from the lunate through both banks of the dorsal portion of the superior temporal sulcus to include both banks of the intraparietal sulcus. A several-mm-square area superior to the intraparietal sulcus at the preoccipital notch was also removed. The ventral limit of the lesion was defined by a line drawn from the tip of the intraparietal sulcus to a point several millimetres below the tip of the Sylvian fissure and then directly in a line perpendicular to the lunate sulcus. On the medial surface the lesion was defined by areas PE and OA extending ventrally almost to the calcarine fissure and including the anterior bank of the parieto-occipital sulcus and all of the tissue rostral to that sulcus for approximately 10 mm.

Following completion of behavioural testing, the monkeys were perfused intracardially under deep barbiturate anæsthesia with saline and 10 per cent formalin, and the brains were blocked stereotaxically in the coronal plane. They were hardened in formalin and 30 per cent sucrose-formalin, embedded in gelatin-albumin, and frozen; 50 μm sections were taken in the coronal plane, then mounted and stained with cresyl violet for microscopic analysis of the lesions. Lateral and medial views of the lesions were reconstructed from enlarged tracing using serial sections every 1 mm. Reconstructions of the individual brains with representative coronal sections through the anterior frontal and posterior parietal lesions are presented in figs. 1 and 2 respectively.

Apparatus

All training was carried out using a PDP-8 computer-controlled DADTA (Discrimination Apparatus for Discrete Trial Analysis; Pribram, 1969). During training the monkey sat in a testing cage measuring 45·72 cm × 50·80 cm × 50·80 cm, one side of which consisted of bars spaced at 4·445 cm intervals. This cage was placed in a small enclosure illuminated by a 15-watt house light in the ceiling. The monkey faced a 50·80 cm × 50·80 cm square panel on which there was embedded a four-by-four regular array of clear round plastic push-panels, 2·54 cm in diameter. Microswitches mounted behind each of the response panels signalled the presses to the computer, and IEE digital display projectors back-projected the stimuli through these panels. A computer program controlled the sequence of stimulus location, the intertrial interval, rewards, and the teletype which recorded the responses. A correct response caused a mechanical feeder to deliver the banana pellet food reward to a single foodwell centred just below the array of response panels. A large one-way mirror permitted observation of the monkey during training.

Procedure

Pre-operatively all monkeys were initially shaped to press only lit panels in the DADTA and were then trained on a colour discrimination problem and its reversal. Post-operatively all monkeys learned three visual discrimination problems (Brody, Ungerleider and Pribram, 1977); each monkey was then assigned to one of four training groups (*see* Tables 1–4). Each training group learned four sets of problems: Personal Spatial (P-Sp); Extrapersonal Spatial (EP-Sp); Internally-ordered Sequences (I-O Sq); Externally-ordered Sequences (E-O-Sq). The training of these problems was counterbalanced such that

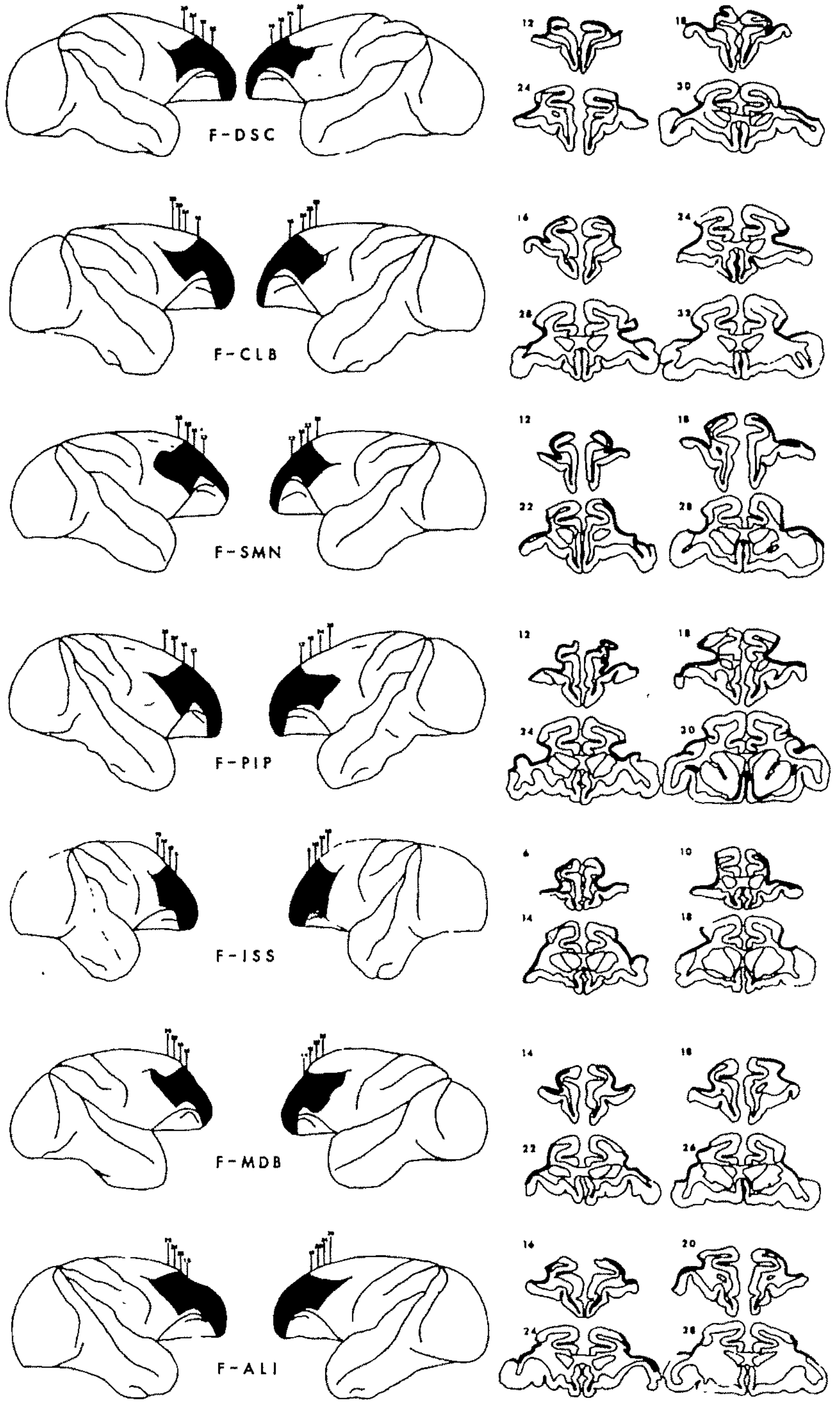


FIG. 1 Anterior frontal lesions. The extent of the individual lesions on the lateral surface was reconstructed from enlarged tracings of the coronal sections taken every 1 mm Four representative coronal sections are presented for each brain The dark line on the coronal sections indicates the extent of damaged or absent tissue

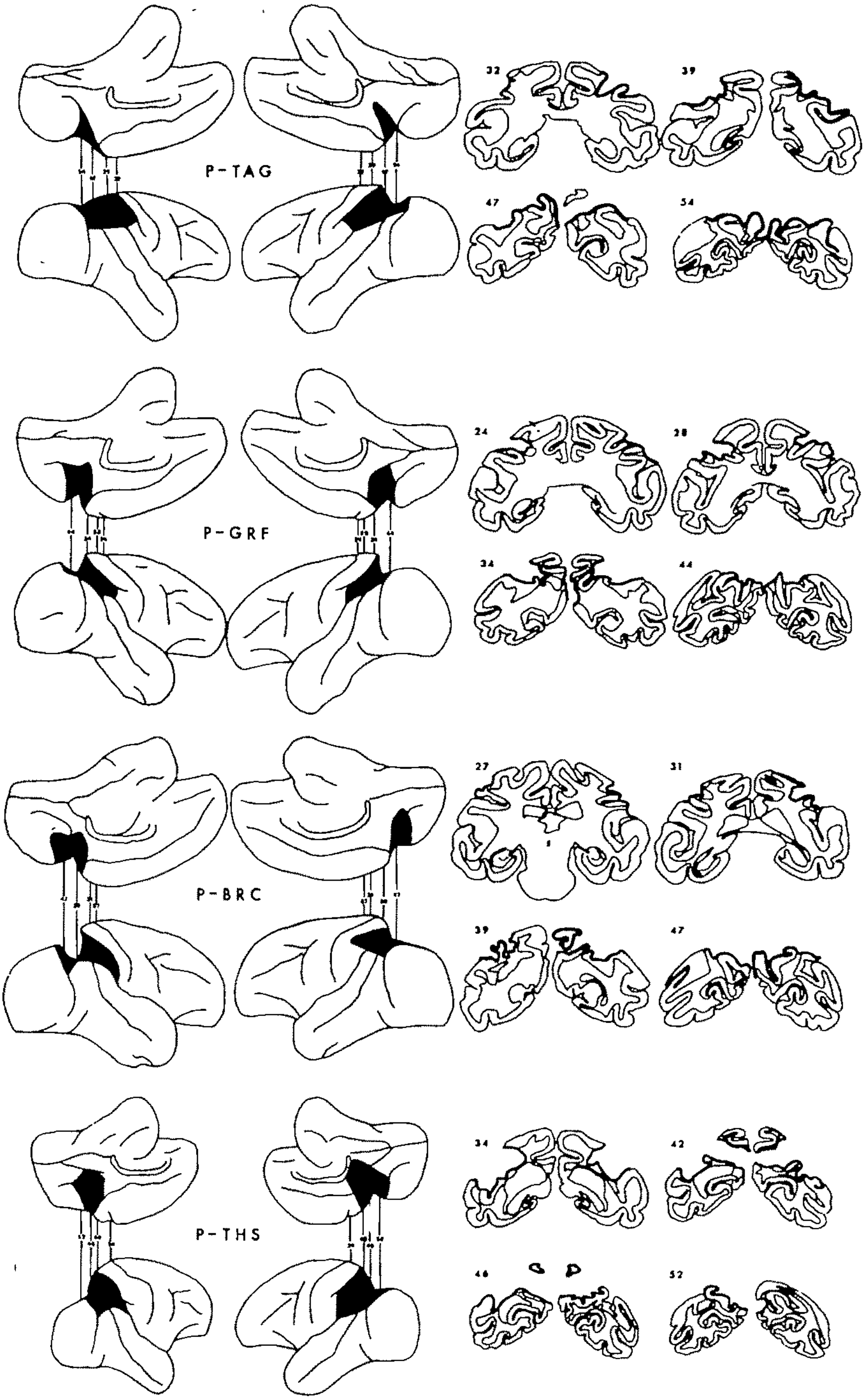


FIG. 2. Posterior parietal lesions. The lateral and medial extents of the individual lesions were reconstructed from enlarged tracings of the coronal sections taken every 1 mm. Representative coronal sections are presented as in fig 1.

Groups A and C learned the spatial problems first and Groups B and D learned the sequences first. The order of training was further counterbalanced as follows:

Training Group A:	EP-Sp	P-Sp	E-O-Sp	I-O-Sq
Training Group B:	E-O-Sq	I-O-Sq	EP-Sp	P-Sp
Training Group C:	P-Sp	Ep-Sp	I-O-Sq	E-O-Sq
Training Group D:	I-O-Sq	E-O-Sq	P-Sp	EP-Sp

Three of the 7 monkeys given frontal resections were trained as members of Group B for the discrimination and sequence problems only; all the other monkeys completed all problems. All monkeys worked 100 trials a day, six days a week to a criterion of 90 correct out of 100 consecutive sets of 10 trials (100 trials) for each problem. Detailed description of the testing procedure follows:

Extrapersonal Spatial Tasks: Free-Start. The monkey was required to press consecutively two (or in the case of the 3-element task, three) contiguous panels in any one horizontal row of the array in order to obtain a pellet. For the initial tasks the monkey was permitted to start anywhere, press a panel, then *press the panel next to the one he had just pressed.* All active and lit panels displayed the stimulus '1' (a white pattern against a dark field). After each correct press the stimuli disappeared, then immediately reappeared as before, except that *the panel the monkey had just pressed turned green.* The trial ended and an eight-second intertrial interval began whenever the monkey made an incorrect press or successfully completed the two or three consecutive presses required. There was no time limit for responding at any point during the trial, but rewards occurred only following the last correct press.

The monkeys were trained in successive steps beginning with just two contiguous panels lit. Since repeat presses were ignored, no errors were possible and only 50 trials were given. The monkeys were then trained to the 90 per cent criterion with 4, 8, and 16 panels lit, beginning with a 2-element version in which they were permitted to start anywhere and then required to press one panel next to their starting panel. They were then trained to the 90 per cent criterion again with 4, 8, and 16 panels lit on a 3-element version in which they were required to press three panels starting anywhere. The third press was correct if it was made directly next to either the first or the second panel just pressed. Three correct presses were therefore not necessarily contiguous presses, but any correct press after the first one was always next to a green panel.

Extrapersonal Spatial Tasks: Forced Random-Start. In order to avoid the tendency of the animals to simply press the same two or three panels each trial, at the beginning of the trial only two panels appeared lit with the '1' stimuli in random positions on the array. A press on either panel caused 15 of the panels to display the '1' stimuli and one of the panels to display a green circle. The monkey was then required to *press the panel next to the green panel* in the same horizontal row. This 2-element version was also followed by a 3-element version in which the first correct press caused all panels to be extinguished and then reappear immediately with 14 of the panels lit with '1's and two consecutive panels lit with green circles. The monkey was again required to press one panel next to either of the green ones. Pressing either a green panel or any other incorrect panel terminated the trial without reward. The initial two '1's, the green cue, and the two consecutive green cues in the 3-element version all appeared in different locations from trial to trial according to three independent pseudo-random sequences. That is, the location of the green cue was independent of the initial press. Thus, all monkeys learned eight versions of the extrapersonal 'next-to' task to the same 90 per cent criterion in the following order: 2-4, 2-8, 2-16, 3-4, 3-8, 3-16, 2-2R, 3-2R. The first number indicates the number of responses required within one trial, the second number indicates the number of consecutive panels initially lit, and the 2R indicates two panels initially lit in random locations on each trial.

Personal Spatial Tasks: Free-Start. This task had exactly *the same requirements as the free-start extrapersonal task.* The monkey was permitted to start anywhere on the array and then required to press two or three consecutive panels in a horizontal line. The third press of the 3-element version was permitted to be next to either the first or the second panel just pressed However, in this task when the monkey pressed a panel, *all of the panel lights disappeared then reappeared exactly as before, that is all displaying '1's.*

Personal Spatial Tasks: Forced Random-Start. As in the extrapersonal random-start version the initial display consisted of only two randomly lit panels. A press on either of these panels caused all 16 panels to display '1's. The monkey was then required to *press the panel next to whichever of the panels he had chosen initially.* For the 3-element version he was required to press three contiguous panels starting with whichever panel he chose initially, and again the third press was permitted to be next to either the first or second panel pressed. In addition, repeat presses were not permitted. Any repeat press as well as any other incorrect press terminated the trial without reward. Again all monkeys learned all eight versions of the personal 'next-to' tasks in the same order: 2-4, 2-8, 2-16, 3-4, 3-8, 3-16, 2-2R, 3-2R.

Thus in both the personal and extrapersonal 'next-to' tasks the monkeys were first trained using a series of displays in which all of the possible response panels were initially lit (free-start versions). The appearance of the display was stable and the monkeys were permitted to establish stable response patterns. They were then transferred to random-start versions of the task in which the relevant stimuli shifted spatial location from trial to trial. This change prohibited the monkeys from using stable response patterns with the same sets of panels every trial.

Externally-ordered Sequential Task. The three problems in the order in which all monkeys learned them were 'red-green' (large solidly coloured circles); '0'-'2'; and '0'-'2'-'6' (white patterns against a dark field). On each trial the two stimuli (or three in the case of the 3-element sequence) appeared in randomly-placed locations on the four-by-four panel array. In order to receive a reward the monkey pressed first the red and then the green panel irrespective of their location. The stimuli disappeared after each press within a trial and reappeared immediately in a new random configuration according to a programmed 100 trial pseudo-random sequence, thereby making spatial strategies irrelevant. The trial ended and an 8-second intertrial interval began when the monkey either made an incorrect press or successfully completed the sequence. There was no time limit for responding at any point in the sequence, but rewards occurred only at the end of a complete sequence.

Internally-ordered Sequential Task. The three problems in the order in which all monkeys learned them were 'blue'-'yellow' (a blue filled plus and a yellow filled triangle); '4'-'5'; and '4'-'5'-'7' (white patterns against a dark field). This task was presented in exactly the same manner as the externally-ordered sequence task except that the monkey was permitted to choose different orders from trial to trial as long as any given sequence contained no repetitions. Thus, for the 2-element 'blue'-'yellow' sequence task either the order of responses blue-yellow or yellow-blue was acceptable. For the 3-element sequence on any given trial there were six acceptable orders: 4-5-7, 4-7-5, 5-4-7, 5-7-4, 7-5-4, and 7-4-5. Because of its difficulty, this last problem was trained for a minimum of 5,000 trials and a maximum of 10,000 trials

RESULTS

Spatial Tasks

The data obtained from the various 'next-to' tasks reveal four striking results:

First, there were no significant differences among any of the groups in the initial free-start version of either the personal or the extrapersonal task (Table 1).

Secondly, on the random-start version of the personal task (fig. 3) the Frontal Group had a deficit compared to both the Normal and Parietal Groups, while the monkeys in the Parietal Group performed well within the normal range. This difference only attained significance for the 3-element version of the task. The Kruskal-Wallis nonparametric one-way analysis of variance by ranks (Siegel, 1956) for three independent samples gave a nonsignificant $H = 0{\cdot}89$ for the two-element version and an $H = 6{\cdot}05$, $P < 0{\cdot}05$ for the three-element version. Paired comparisons using the Mann-Whitney U test for two independent samples (Siegel, 1956) indicated that this overall group difference was due to the poor performance of the monkeys with frontal lesions. The comparison of the Frontal and Parietal Groups gave a U = 0, $P = 0{\cdot}014$, and the comparison of Frontal and Normal Groups gave a U = 1, $P = 0{\cdot}057$.

TABLE 1. TRIALS TO 90 PER CENT PERFORMANCE LEVEL
'NEXT-TO'
FREE-START TASKS

Subjects	*Training Group*		*Extrapersonal*		*Personal*	
			2-press	*3-press*	*2-press*	*3-press*
N-Lns	A		90	250	50	70
N-Zld	B		80	100	60	0
N-Gld	C		90	170	2640	1830
		Mean	87	173	917	633
P-Brc	A		320	190	20	30
P-Ths	B		230	160	150	310
P-Grf	C		30	680	880	1510
P-Tag	D		0	0	230	100
		Mean	145	258	320	488
F-Dsc	A		450	470	310	2070
F-Pip	B		250	20	100	430
F-Smn	C		90	0	2890	8630
F-Clb	D		0	0	310	0
		Mean	198	122	902	2782

* N = Normal Group; P = Parietal Group; F = Frontal Group.

Thirdly, on the random-start versions of the extrapersonal task (fig. 4) both the Frontal and Parietal Groups demonstrated a significant impairment compared to the normal performance. The Kruskal-Wallis analysis of variance indicated significant overall differences among the three groups for both the two-element and three-element versions of the task. For the 2-element version H = 6·20, $P < 0{\cdot}05$, and for the 3-element version H = 6·40, $P < 0{\cdot}05$. For the 2-element version the Mann-Whitney U test gave a U = 0, $P < 0{\cdot}028$ for comparisons between both the Frontal and Normal Groups and between the Parietal and Normal Groups. For the 3-element versions the comparison between the Parietal and Normal Groups gave a nonsignificant U = 2, $P = 0{\cdot}114$. There was complete overlap between the Frontal and Parietal groups on both versions of the extrapersonal 'next-to' tasks.

Fourthly, on the random-start tasks, the performance of all monkeys, including the impairment shown by the Frontal Group, was independent of the level of testing sophistication they had attained prior to beginning these tasks. On the free-start

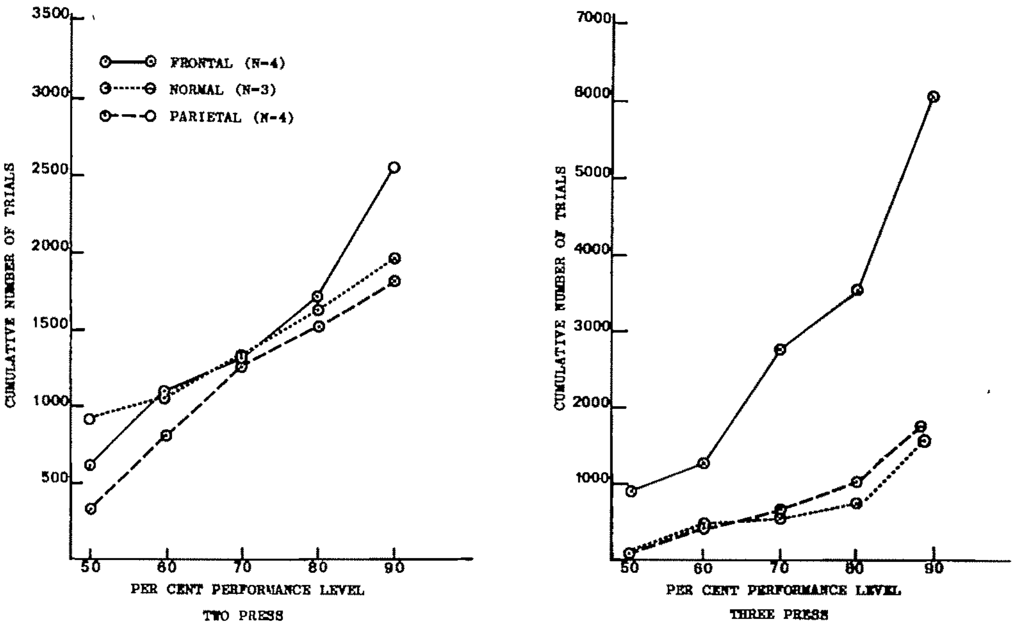


FIG 3 Personal 'next-to' task. The cumulative number of trials required to reach each successive performance level (percentage correct) during acquisition of two versions of the task are presented for each experimental group. Two-press version—initialize press, then press the panel next to the panel just pressed. Three-press version—initialize press, then press the panel next to the panel just pressed, then press the panel next to either one of the two panels just pressed. All monkeys learned the two-press version first and then the three-press version.

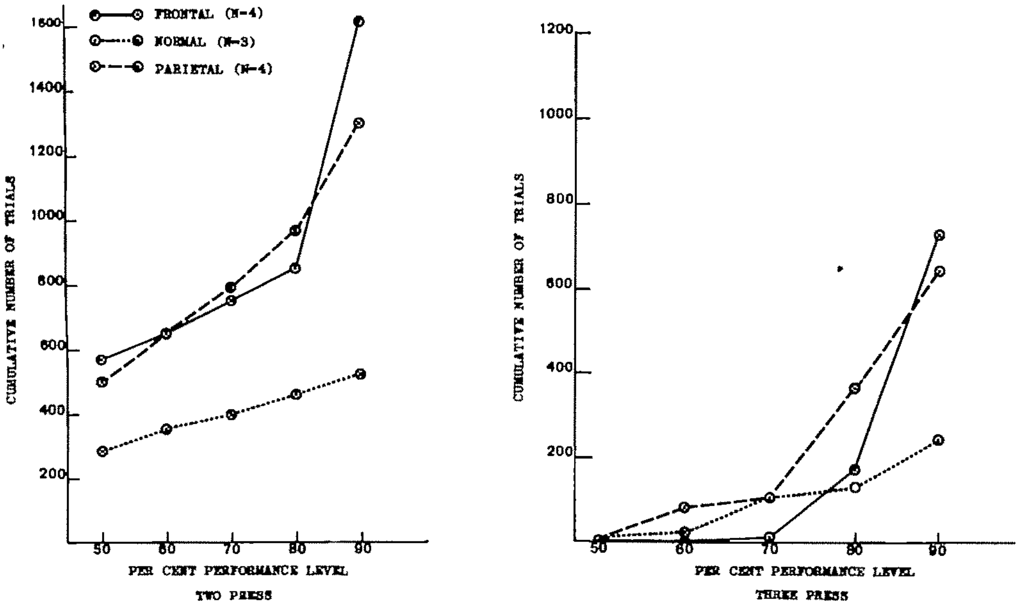


FIG. 4. Extrapersonal 'next-to' task Learning curves are presented as in fig 3 Two-press version—initialize press, then press the panel next to the single green panel Three-press version—initialize press, then press the panel next to the single green panel, then press the panel next to either one of the two adjacent green panels. All monkeys learned the two-press version first and then the three-press version

tasks there was a significant tendency for the monkeys who learned the extrapersonal tasks before the personal tasks (Training Groups A and B) to reach criterion more slowly ($U = 2$, $P = 0{\cdot}02$, $N_{1,2} = 6,5$ two-tailed) on the extrapersonal tasks and more quickly on the personal tasks ($U = 1$, $P = 0{\cdot}008$) than those who learned the tasks in the reverse order (Training Groups C and D). However, there were no differences among the lesion groups in this tendency, and the effect became insignificant by the 3-element version of each task. Similar comparisons for the random-start tasks indicated extensive overlap among the performances of the training groups (Table 2).

TABLE 2. TRIALS TO 90 PER CENT PERFORMANCE LEVEL
'NEXT-TO'
RANDOM-START TASKS

	Training		*Extrapersonal*		*Personal*	
Subjects	*group*		*2-press*	*3-press*	*2-press*	*3-press*
N-Lns	A		530	0	340	610
N-Zld	B		480	490	1680	2570
N-Gld	C		550	230	3890	1530
		Mean	520	240	1970	1570
P-Brc	A		820	10	1520	510
P-Ths	B		1910	640	2720	1790
P-Grf	C		980	850	2310	2310
P-Tag	D		1470	1080	780	2180
		Mean	1295	645	1832	1698
F-Dsc	A		2630	1360	2160	2550
F-Pip	B		880	630	2090	3100*
F-Smn	C		1350	330	2330	13580
F-Clb	D		1590	600	3620	5130
		Mean	1612	730	2550	6090

* Training stopped after 80 per cent but before 90 per cent criterion attained.

In order to detect any further difference in the nature of impairments produced by frontal or parietal cortical damage, several types of error analyses were performed on the data from the random-start versions of both 'next-to' tasks.

While learning the personal task the monkeys made many of their errors by pressing the other one of the two 'initialize' panels. The number of incorrect presses on the 'other-initialize' panel was tallied for the first 100 non-repeat errors made in learning the 2-element version. The expected frequency of such an error in 100 trials is 7. The means of the observed frequencies for the Normal, Parietal, and Frontal Groups gave Z scores respectively of 9·04, 16·7, and −0·2. That is, both the monkeys of the Parietal and Normal Groups, but not the Frontal Group, made significantly more of such errors than would be expected by chance.

For the extrapersonal 'next-to' task where the Frontal Group was as impaired as the Parietal Group, none of the error analyses revealed any differences in behavioural strategies. The first 100 trials in which each monkey made exactly 50 correct responses were tallied according to the location to the right or left of the green cue for the correct responses and the spatial location for the incorrect responses. The data indicated that all monkeys distributed their correct responses relatively equally to the right and left of the green cue, and there were no group differences. There were no differences among the groups in the tendency to incorrectly respond to the green cue itself, to incorrectly press panels that were on the same horizontal row but separated from the cue by one panel, or to incorrectly press panels that were vertically or diagonally next to the cue. Furthermore, there were no differences among the groups in the tendency to continue incorrectly pressing the panel next to the 'initialize' panel.

Sequence Tasks

The data from both the externally-ordered and internally-ordered sequence problems reveal several striking results. *First, the level of sophistication was quite clearly the most important variable in determining the ease with which rhesus monkeys were able to learn such sequences regardless of the type of brain damage they sustained. Second, the monkeys with frontal ablations showed a striking impairment which was dependent on their level of sophistication.*

However, sophistication apparently needs to be defined differently for the two types of sequences. In the case of the externally-ordered sequences, any extended experience with the automated apparatus produced sophistication. Not only did the two training groups (C and D) which had learned the internally-ordered sequences first perform well on the externally-ordered sequences, but the monkeys in Group A, who had finished the spatial tasks, also performed equally well despite the fact that the externally-ordered sequences were the first sequences they experienced (Table 3). In the case of the internally-ordered sequences, general sophistication apparently did not suffice. Only those two training Groups (A and B) which had previously learned externally-ordered sequences were able to learn the two 2-element sequences significantly faster than either of the other two training groups regardless of their level of general sophistication (Table 4).

The learning curves of the monkeys with parietal damage showed complete overlap with the curves of the normal monkeys at each criterion level; this was true for both the sophisticated and the naive monkeys (*see* Tables 3 and 4). Therefore, in order to determine which factors were contributing to the differences between the groups, two-way analyses of variance were calculated on each of the sequences at the 90 per cent criterion level with the Parietal and Normal Groups combined to form a single Control Group. The two factors analysed were (a) level of sophistication and (b) presence or absence of frontal cortical damage. A significant effect due to level of sophistication was obtained on the three easiest of the six sequences trained; that is, the 'red'-'green' ($F = 48{\cdot}8$, d.f. $= 1/10$, $P < 0{\cdot}001$)

TABLE 3. TRIALS TO 90 PER CENT PERFORMANCE LEVEL EXTERNALLY-ORDERED SEQUENCE TASKS

Subjects	*Training group*		*Red-green*	*0-2*	*0-2-6*
Naive					
N-Zld	B		1780	670	4150
P-Ths	B		1990	670	4380
		Mean	1885	670	4265
F-Iss	B		2420	1100	5160
F-Pip	B		2180	2040	12160
F-Ali	B		2410	2050	4000
F-Mdb	B		2880	1670	6670
		Mean	2472	1715	6998
Sophisticated					
N-Lns	A		610	590	1400
N-Gld	C		1520	830	7180
N-Brc	A		370	550	2830
P-Grf	C		410	140	1400
P-Tag	D		680	600	4570
		Mean	748	542	3476
F-Dsc	A		390	630	2380
F-Smn	C		640	670	4830
F-Clb	D		1060	110	3030
		Mean	697	470	3413

and the ‘0’-‘2’ ($F = 14$, d.f. $= 1/10$, $P < 0{\cdot}004$) externally-ordered sequences and the ‘blue’-‘yellow’ ($F = 42$, d.f. $= 1/10$, $P < 0{\cdot}001$) internally-ordered sequence. There was both a significant lesion effect and a significant interaction between level of sophistication and lesion for the ‘0’-‘2’ sequence ($F = 7{\cdot}1$, d.f. $= 1/10$, $P < 0{\cdot}024$; and $F = 9{\cdot}3$, d.f. $= 1/10$, $P < 0{\cdot}012$ respectively) and for the ‘blue’-‘yellow’ sequence ($F = 12{\cdot}9$, d.f. $= 1/10$, $P < 0{\cdot}005$; and $F = 10$, d.f. $= 1/10$, $= < 0{\cdot}010$ respectively).

Specific comparisons indicate that naive monkeys with frontal ablations had a significant deficit in reaching the 90 per cent criterion compared to the naive controls; for ‘red’-‘green’ ($t = 2{\cdot}56$, d.f. $= 4$, $P < 0{\cdot}05$); for ‘0’-‘2’ ($t = 3{\cdot}12$, d.f. $= 4$, $P < 0{\cdot}05$); and for ‘blue’-‘yellow’ ($t = 2{\cdot}54$, d.f. $= 3$, $P < 0{\cdot}05$). In contrast, the sophisticated monkeys with frontal ablations performed extremely well. Their learning scores were completely within the range of those of the sophisticated monkeys from the Parietal and Normal Groups. The differences between the mean scores of the naive and sophisticated monkeys with frontal ablations were highly significant; for ‘red’-‘green’ ($t = 7{\cdot}44$, d.f. $= 5$, $P < 0{\cdot}005$); for ‘0’-‘2’ ($t = 4{\cdot}09$, d.f. $= 5$, $P < 0{\cdot}005$); and for ‘blue’-‘yellow’ ($t = 5{\cdot}01$, d.f. $= 5$, $P < 0{\cdot}005$).

TABLE 4. TRIALS TO 90 PER CENT PERFORMANCE LEVEL INTERNALLY-ORDERED SEQUENCE TASKS

Subjects	*Training group*		*Yellow-blue*	*4-5*
Naive				
N-Gld	C		1390	9450
P-Grf	C		2510	350
P-Tag	D		3320	2200
		Mean	2406	4000
F-Smn	C		4700	4230
F-Clb	D		8900	1320
		Mean	6800	2775
Sophisticated				
N-Lns	A		30	80
N-Zld	B		500	240
P-Brc	A		140	790
P-Ths	B		310	330
		Mean	245	360
F-Dsc	A		90	290
F-Iss	B		20	—
F-Pip	B		50	7040
F-Ali	B		610	650
F-Mdb	B		1830	—
		Mean	520	2660

The learning curves for the three externally-ordered sequences (fig. 5) suggest that the naive controls became sophisticated faster than the naive monkeys with frontal ablations. However, there were too few subjects in the Control Group for the interaction effect to attain statistical significance in a three-way analysis of variance with repeated measures on the three sequence problems.

The ease with which each monkey was able to solve the internally-ordered sequences correlated highly with the degree to which the monkey limited the number of possible sequences he actually used during a session. The monkeys were ranked according to the number of times each monkey used the same one of the two possible correct sequences during the first 100 trials in which he made exactly 90 correct responses. The Spearman rank correlation (two-tailed) between that ranking and the ranks on trials to a 90 per cent criterion was Rho $= 0{\cdot}68$, $P < 0{\cdot}01$ for 'blue'-'yellow' and Rho $= 0{\cdot}63$, $P < 0{\cdot}05$ for '4'-'5'. The sophisticated monkeys had means of 88 and 87 responses of the same order for the 'blue'-'yellow' and '4'-'5' sequences respectively while the naive monkeys had respective means of only 62 and 69 responses of the same order. Moreover, those monkeys who had previously learned the fixed sequence 'red'-'green' began the 'blue'-'yellow' sequence

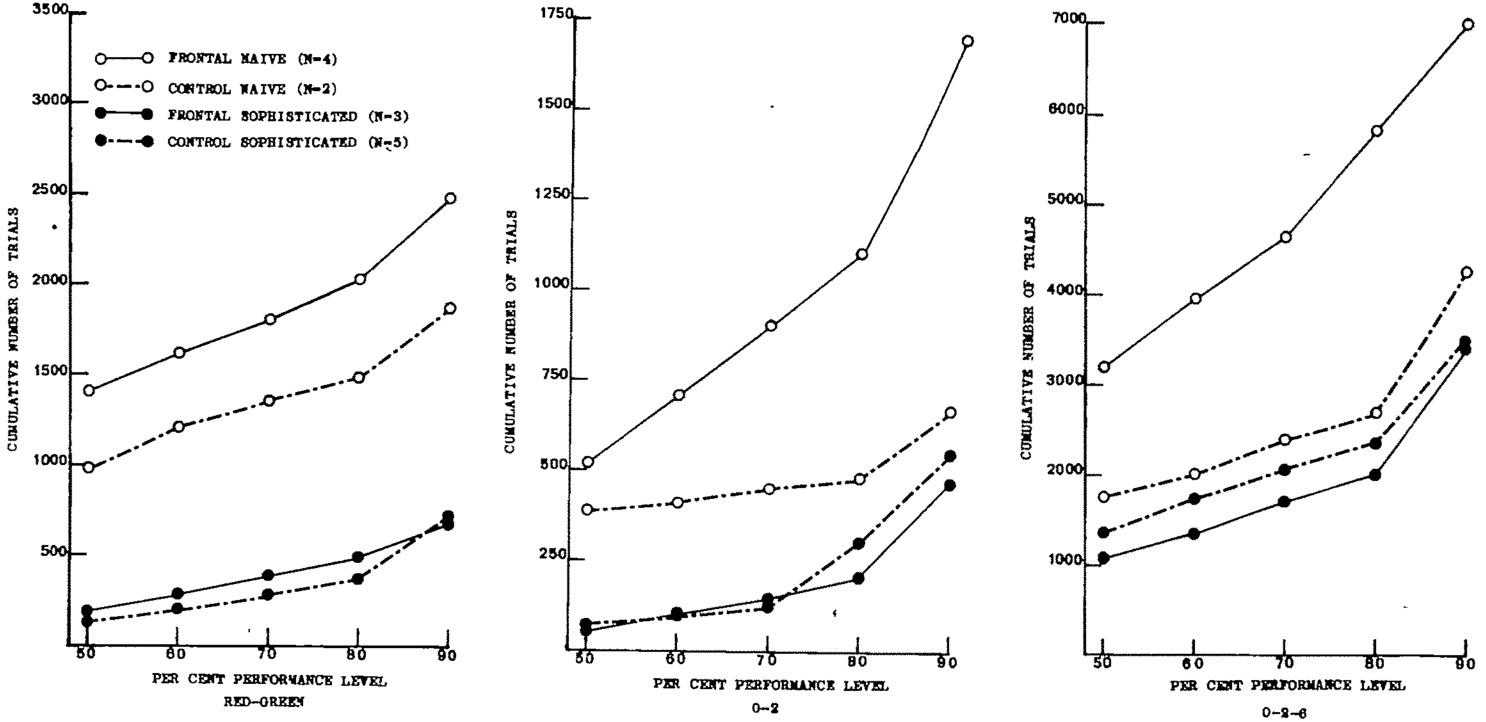


FIG 5. Externally-ordered sequence tasks. The cumulative number of trials required to reach each successive performance level (percentage correct) during acquisition of the three sequence problems are presented separately for the naive and sophisticated Frontal and Control Groups The Control Group consists of the monkeys with parietal lesions and the normal monkeys. All monkeys learned all three problems in the order 'red'-'green', '0'-'2'; '0'-'2'-'6'

using almost exclusively the yellow-blue order even though either order was correct. There was no particular tendency for the monkeys with frontal ablations to limit the number of possible sequences they used more or less than the control monkeys. Only 3 (one monkey each from the naive Frontal, sophisticated Frontal, and sophisticated Parietal Groups) of the 11 monkeys trained on the 3-element internally-ordered sequence showed any tendency to limit their choices among the six correct possible sequences. Each of these 3 showed a significant tendency to begin the trial with the stimulus '5'. Moreover, these 3 plus one additional normal sophisticated monkey were the only monkeys able to reach an 80 per cent criterion within the allotted 10,000 trials. The remaining 8 monkeys required between 7,000 and 10,000 trials to reach a performance level of 70 per cent correct, and there was complete overlap in the learning curves of all training groups regardless of lesion or level of sophistication.

For the 3-element externally ordered sequence there were six possible incorrect responses: '2', '6', '0'-'0', '0'-'6', '0'-'2'-'0', and '0'-'2'-'2'. For the 3-element internally-ordered sequence there were three types of incorrect responses: XX, XYY, or XYX. An analysis of the type of error made at the 50 per cent performance level for both sequences also failed to reveal any consistent differences among groups.

DISCUSSION

Spatial Tasks

The purpose of this part of the study was to re-examine the relevance of a personal-extrapersonal spatial dichotomy to frontal and parietal cortical function by training monkeys on conceptually simple 'next-to' tasks. The results did not provide the double dissociation predicted by this dichotomy: while the Parietal Group was impaired only on the extrapersonal 'next-to' task, the Frontal Group was impaired on both the personal and extrapersonal 'next-to' tasks, but only under a random-start condition.

The fact that the monkeys of the Parietal Group were significantly impaired on a task which required them to press a panel next to a green cue but were unimpaired on a more difficult task which required them to press the panel next to their own previous press supports the usefulness of the extrapersonal-personal spatial distinction with respect to parietal function. It is true that the Parietal Group did not show the expected deficit on the initial free-start version of the extrapersonal task. However, in that version the 'initialize' panel itself became green so that the task could be solved by ignoring the green cue and simply pressing the panel next to the 'initialize' panel, that is, by treating the task as if it were a personal 'next-to' task. It is interesting that these findings from monkeys parallel the findings from patients with parietal damage confined to the right hemisphere. Such patients show only extrapersonal spatial deficits even though patients with left parietal damage show both personal and extrapersonal spatial deficits (Semmes *et al.*, 1963; Teuber, 1964; Butters *et al.*, 1973).

The surprising result in this study was that the Frontal Group was as impaired as the Parietal Group on the random-start extrapersonal 'next-to' task. Neither an emphasis on spatial memory impairments (Goldman *et al.*, 1971) nor on personal spatial orientation (Semmes *et al.*, 1963; Pohl, 1973) would have predicted that monkeys with frontal damage should have any deficit on a task which simply required the monkey to press a panel next to a visible green cue. The task required neither memory nor personal orientation.

The importance of the spatial factor with respect to frontal cortical control mechanisms was first suggested by Mishkin and Pribram (1955, 1956) when they found that several non-spatial variations of the delayed-response and delayed-alternation tasks improved the performance of monkeys with frontal resections. Although a spatial hypothesis became less tenable when they next demonstrated that frontal resections produced deficits on an extremely difficult right-left alternation task that were as severe as those on spatial alternation, an unusually good performance on object alternation by one monkey in the Frontal Group called for further analysis (Pribram and Mishkin, 1956). To this end, Pribram (1961) devised a multiple location object alternation test which was more readily learned by monkeys. However, he continued to find a deficit after frontal lesions although performance (70 per cent) was better than on spatial alternation (50 per cent). Mishkin, Vest, Waxler and Rosvold (1969), using Pribram's new test, then found a dissociation between object and spatial alternation by making more restricted resections within the frontal cortex. They demonstrated that monkeys with lateral frontal resections confined more dorsally to the region of the sulcus principalis continued to have a profound deficit on spatial alternation but were able to attain a performance level of 80 per cent on object alternation. In contrast their monkeys with more 'ventral' resections, including both orbitofrontal and ventrolateral frontal cortex showed profound deficits on both the spatial and object alternation tasks suggesting the monkeys were disturbed by the reversal factor involved in both tasks.

These results indicate that different functions may be differentially localized within the frontal cortex. Despite this, we chose to utilize the larger dorsolateral resection defined by the projection of the parvicellular portion of the *nucleus medialis dorsalis* (Pribram, Chow and Semmes, 1953) thus invading the ventrolateral cortex. This choice was made because we wanted to evaluate both spatial factors (on the basis of the above data presumably located around the *sulcus principalis*) and temporal factors (possibly located more ventrally). As we were interested in analysing the nature of the deficit rather than its localization, we utilized the small number of subjects available to such a study to control for test variables rather than to subdivide the group according to a variety of lesions. However, because the resections did include the entire anterior lateral surface, possible effects specifically due either to damage to the frontal eye fields (area 8) or to invasion of the ventrolateral surface must be considered.

Results of earlier studies indicate that an explanation in terms of peripheral inattention or neglect due to damage to the frontal eye field is unlikely to account for the observed data. Monkeys with unilateral damage to area 8 do demonstrate transient neglect of the contralateral visual field, but they do not show neglect after bilateral damage (Kennard, 1939; Pribram, 1955). Presumably if frontal damage caused an attentional neglect of the peripheral field of vision, the errors made by the Frontal Group would centre around whatever point on the response panel array the particular monkey tended to fixate. Fixation points were not measured in this study; however, the Frontal Group demonstrated the same error patterns as did the Parietal and Normal Groups on the extrapersonal 'next-to' task. This pattern of error was in fact random with respect to both the green cue and the 'initialize' panel.

Mishkin and others have postulated that the ventrolateral surface is part of the frontal cortical region in which damage produces perseverative interference (Mishkin, 1964; Butter, 1969; Iversen and Mishkin, 1970; Passingham, 1972). In the present study, the method of training the monkeys to learn the extrapersonal 'next-to' task involved a shift from the free-start version in which the green cue appeared on the panel the monkey had just pressed (necessitating a response to the panel next to the first press) to a random-start version in which the green cue appeared in random locations (generally necessitating responses away from the 'initialize' panel). This shift in the response pattern requirement could have created deficits due to perseverative response tendencies. However, error analyses revealed that there were no differences among groups in the tendency to perseverate the response next to the 'initialize' panel. By the time the monkeys had attained a 50 per cent correct performance level such perseverative errors constituted less than 15 per cent of the errors for each group. Furthermore, when the monkeys from this study were trained on a landmark reversal problem, the Frontal Group demonstrated a normal performance (Ungerleider and Brody, 1977). Reversal learning tasks in general have been shown to be extremely sensitive to perseverative interference errors (Mishkin, 1964; Iversen and Mishkin, 1970). Therefore, if the monkeys had sustained sufficient damage to the ventrolateral surface to account for their deficits on the basis of perseverative interference, they should also have demonstrated significant perseverative interference on the landmark reversal task.

Thus neither a peripheral inattention hypothesis nor a perseverative interference hypothesis adequately accounts for the data. However, other details of the performance of the monkeys with frontal lesions suggest an alternate explanation for the unexpected difficulty the Frontal Group had with the random-start extrapersonal task.

First, the data indicate that the Frontal Group demonstrated an impairment on the personal 'next-to' tasks only if the 'initialize' cues shifted spatial location randomly from trial to trial and only during the 3-element version of the task. Observation of the monkeys during the learning of this task indicated that this impairment was due to their inability to flexibly shift their response patterns from a left-right movement to a right-left movement, or *vice versa*, when the location of the 'initialize' cues on the response-panel display demanded the direction of movement opposite to the individual monkey's preferred direction. Only the 3-element version in which three consecutive panels had to be pressed within a four-panel row required frequent shifts in the response pattern.

In addition, still other aspects of the data indicate that the Frontal Group might have been relying heavily on movement stereotypes to solve the personal 'next-to' task. When the monkeys were first learning the task, the Frontal Group made significantly fewer errors by pressing the other one of the two 'initialize' panels than either the Normal or Parietal Groups. Unlike the other monkeys, they made that error at chance frequency. The occurrence of such an error at a level greater than would be expected by chance implies that the monkey remembered correctly where the location of the stimulus was before all the panels became identically lit. The fact that the Frontal Group showed no evidence of remembering where the initialize cues had been strongly suggests that their normal performance on the random-start 2-element personal task was dependent on movement stereotypes learned in the initial free-start versions. Moreover, the lack of a significant group effect in the 2-element random-start task was due more to the increased variance of the ability of the Normal Group to solve this more difficult task than to a particularly inspired performance by the Frontal Group.

Thus, the ability of the monkeys in the Frontal Group to depend on movement stereotypes could explain their normal performance on the free-start and the 2-element random-start personal task. These movement patterns failed in the 3-element version of the personal 'next-to' task specifically because flexibility of response was required. Perhaps then the deficits of the Frontal Group were *unrelated* to spatial processes in both the personal and extrapersonal 'next-to' task.

Recent neurophysiological findings provide evidence relevant to this question. There is a population of single units in posterior parietal cortex which responds when arm movements towards relevant stimuli are co-ordinated with visual fixation of those stimuli in space (Hyvarinen and Poranen, 1974; Mountcastle, Lynch, Georgopoulos, Sakata and Acuna, 1975). These data support the view that the posterior parietal region is specifically concerned with spatial orientation. In contrast single units in dorsolateral frontal cortex do not respond in relation to arm movements but rather respond when the monkey must *hold* relevant information *in memory* prior to making a response in a delayed response or delayed alternation paradigm (Fuster, 1973; Kubota and Niki, 1971; *see also* Stamm and Rosen's macroelectrode analysis, 1969). Thus neurophysiological data as well as the behavioural data of this study suggest that the frontal cortex is involved in higher-order control functions. Such functions are easily tapped by personal spatial tasks but may also be tapped by other problems, such as the extrapersonal 'next-to' task and the sequence tasks which constitute the other part of this report.

Sequence Tasks

The purpose of this part of the study was to evaluate the importance of anterior frontal cortex in controlling sequences of behaviour when such sequences are completely independent of spatial location and to re-examine the effect of forcing a monkey to internally organize his own sequence at each trial rather than providing him with a predetermined externally imposed set of rules to guide his responses.

The results indicate that *neither spatial memory nor* the different types of *temporal memory* demands inherent in the two kinds of sequence problems *are critical factors* in determining the ability of monkeys with anterior frontal ablations to solve complex problems. First, the naive Frontal Group demonstrated a clear impairment in learning both the externally and simplest internally-ordered sequences, but that impairment did not appear on any of the sequence problems if the monkeys had previously acquired extensive testing experience. Second, regardless of presence or locus of lesion the sophisticated monkeys learned the externally-ordered sequences significantly faster than the naive monkeys.

With respect to the externally-ordered sequence the results of this study are therefore in agreement with those of the study by Pinto-Hamuy and Linck (1965), but they provide an alternative explanation. The monkeys in that earlier study all had had extensive experience with internally-ordered sequence problems prior to learning the externally-ordered sequence. Hence they were sophisticated by the definition used here, and like the monkeys in the present study, the Frontal Group learned the latter sequence as quickly as the normal controls.

Pinto-Hamuy and Linck had concluded on the basis of their results that monkeys with frontal ablations are impaired on sequence problems specifically when the elements of the sequence must be internally ordered by the monkey. However, it now appears that there are three possible factors which could account for the poor performance of the Frontal Group on their internally-ordered tasks: (1) the task-tested spatial memory; (2) the internally-ordered sequence task required a different type of memory organization than the externally-ordered sequence task; and (3) the monkeys had no prior DADTA testing experience, and were therefore naive.

The results of the present study suggest that in fact the third factor was the critical one. First, the spatial memory factor can be ruled out since the present data indicate that under certain conditions the Frontal Group showed a significant impairment on sequence problems even though demands on spatial memory had been eliminated. It is more difficult to rule out one or the other of the remaining two possibilities on the basis of the current results. Although general testing experience with the DADTA enabled all of the monkeys to learn the externally-ordered sequences quickly, it was not sufficient to enable them to learn the internally-ordered sequences quickly. For these latter sequence problems only those monkeys who had learned the former sequence problems were aided by their previous testing experience, and in those cases the transfer seemed to be directly from performing the 'red'-'green' sequence in the required order red-green to invariantly performing the 'blue'-'yellow' sequence in the order yellow-blue. The effect of sophistication therefore seemed mainly to predispose the monkeys towards restricting their own alternatives. Such restrictions actually changed the internally-ordered sequences into externally-ordered ones. It is therefore impossible to determine from the data if an intact frontal cortex would have been necessary to allow the monkey to perform the internally-ordered sequences normally while choosing different orders for those sequences on each trial. The data do indicate that when faced with such difficult sequences the sophisticated Frontal Group was able to impose the restrictions on their own choices as quickly as the sophisticated Control Group. Thus there is some evidence that the critical factor in determining the relative performance of the Frontal Group was not the type of memory required by the sequence tasks but rather was the level of testing experience in the DADTA the monkeys had attained before beginning any particular sequence.

If the previous level of testing experience affected the performance of the Frontal Group more than that of the Control Group, the implication is that frontal cortical ablations made the monkeys less able to integrate or compensate for some feature of the training situation. That feature appears to be the continuous shifting of the spatial location of the stimuli. Like the solutions to the random-start 'next-to' problems, the solutions to the sequences were made independent of absolute spatial location by having the stimuli appear in random spatial locations from step to step within each trial. Moreover, this same Frontal Group showed a significant deficit in learning simultaneous two-choice discrimination problems in the DADTA where again the stimuli appeared in random spatial locations from trial to trial but learned similar problems at a normal rate in a Wisconsin General Testing Apparatus where the stimuli remained within the same two locations each trial (Brody, Ungerleider and Pribram, 1977).

Concluding Remarks

The normal performance of the Frontal Group on the initial and the 2-element personal 'next-to' tasks and of the sophisticated members of the Frontal Group on the sequences indicate that neither sequencing *per se* nor personal spatial orientation or spatial memory *per se* is dependent on intact functioning of the frontal cortex. The frontal cortex must be involved in higher-order control of stimulus-response correlation and organization.

A clue to the nature of that higher-order function lies in the difference between the good performance of the monkeys with frontal damage on the free-start versions and their consistent poor performance on the random-start versions of both the extrapersonal and personal 'next-to' tasks. The critical factor producing the frontal deficit on the 'next-to' tasks is the variable nature of the relevant stimulus or the required response—in one case the location of the green cue and in the other the starting location or the direction of movement required.

Moreover, the data strongly suggest that damage to the frontal cortex causes monkeys to be adversely affected by lack of stability in the spatial location of relevant stimuli even when the spatial location provides a context which is irrelevant to the solution of the problem. In order to solve the sequence problems the monkey must learn that the spatial context is not relevant; he must eliminate all hypotheses based on spatial location. However, if the monkey is especially sensitive to spatial distractors, he will have greater difficulty in learning to ignore that aspect of the stimuli. An earlier study utilizing the DADTA (Grueninger and Pribram, 1969) had indicated that irrelevant spatial distractors (an irrelevant stimulus appearing in novel spatial locations) were particularly potent in disrupting the performance of monkeys with frontal ablations on a well-learned task. The present study suggests that when the variable aspects of the stimuli are irrelevant, the disruptive effect of such variability can eventually be circumvented even by monkeys with frontal lesions. When the monkeys with frontal damage finally did learn to ignore the irrelevant shifting spatial context, they had no further difficulty in learning nonspatial discrimination problems (Brody, Ungerleider and Pribram, 1977) or in ordering nonspatial sequences. This ability to eventually ignore irrelevant spatial variabilities may explain why such monkeys are better able to learn object alternations than spatial alternations (Pribram, 1961; Mishkin *et al.*, 1969) despite the fact that both tasks represent unparsed sequences of regularly varying correct choices.

In contrast to the sequence problems, the critical issue for the 'next-to' problems was where to press, not what to press. The spatial context remained relevant to the solution of the problem, but that context varied from trial to trial. It is interesting that although the solution required abstracting the concept of relative spatial position, 'next-to', it was the shifting of the absolute spatial locations which constituted the unreliable context. Thus, in the current 'next-to' tasks, just as in the case of the delayed-response task where the spatial context is relevant but unreliable (Anderson, Hunt, Vander Stoep and Pribram, 1976), frontal damage produced a deficit. The data therefore indicate that *the frontal cortex is essential to the ability to perform tasks in which context varies.* This ability is essential to allow flexibility in response (Pribram, *et al.*, 1964) appropriate to the demands of such tasks. The effect of frontal damage can be seen as a lack of flexibility of response when the context prohibits stable or routine response patterns (as with the 3-element personal 'next-to' task) or it can be manifest as a deficient ability to abstract the relevant stimulus parameters when the cues constituting context vary (as in the sequence tasks, discrimination problems, or the extra-personal 'next-to' task). The interpretation of the current finding as indicating that frontal cortex is essential to an ability to perform tasks in which context varies is not only consistent with other data obtained from monkeys but also provides a framework for understanding the classic finding that patients with damage to the frontal cortex have difficulty generating flexible response patterns in the face of changing environmental demands (for example, Ackerly and Benton, 1948; Milner, 1964; Pribram, *et al.*, 1964; Luria, 1966).

SUMMARY

Normal monkeys and monkeys with resection of anterior frontal or posterior parietal cortex were trained to press a panel next to a green panel as a test of extrapersonal spatial orientation and to press a panel next to their own prior press as a test of personal spatial orientation. All monkeys also learned two sets of sequence problems in which the solutions were made independent of spatial location by randomly shifting the locations of the stimuli after each response within a trial. The Parietal Group was significantly impaired on the extrapersonal 'next-to' task but not the more difficult personal 'next-to' task. The Frontal Group was impaired on both the personal and the extrapersonal 'next-to' tasks but only when the relevant cues shifted spatial locations from trial to trial. The performance of the Parietal Group completely overlapped that of the Normal Group on the sequence problems regardless of the level of testing sophistication the monkeys had attained. In contrast, the Frontal Group demonstrated a significant impairment in learning sequences but only when the monkeys were naive. Once they became sophisticated, they learned each sequence at a normal rate. Their poor performance was attributed to the lack of stability in the spatial location of the stimuli. The data support the view that a distinction between personal and extrapersonal spatial orientation is relevant to posterior parietal function but indicate that neither sequencing *per se* nor personal spatial orientation or spatial memory *per se* is dependent on intact frontal functioning. Rather, the frontal cortex is involved with a higher-order control essential to allow the monkey to perceive the reliable aspects of stimuli contained in a stimulus context full of unreliable noise and to further allow for flexible response pattern appropriate to the demands of a variable context.

ACKNOWLEDGEMENTS

The authors wish to express appreciation to Dr. Leslie Ungerleider for her criticisms and assistance in the preparation of this manuscript, to Angela DiBerardino for histological assistance, to Karl Drake for technical assistance, to Bruce Rule for computer programming, and to Dr. Helena Kraemer, Hugh McDonald, and Dr. Benjamin Dawson for assistance with the statistical analysis. This research was supported by National Institute of Mental Health Grants 12970-11 and K6-15214 to Karl H. Pribram and National Institute of Mental Health Predoctoral Fellowship HSMHA 1501MH 54525 to Betty Ann Brody and was part of the doctoral dissertation for the Ph.D. granted to Betty Ann Brody by Stanford University.

REFERENCES

ACKERLY, S. S. and BENTON, A. L. (1948) Report of case of bilateral frontal lobe defect. *Research Publications. Association for Research in Nervous and Mental Diseases*, 27, 479–504.

ANDERSON, R. M., HUNT, S. C., VANDER STOEP, A. and PRIBRAM, K. H. (1976) Object permanency and delayed response as spatial context in monkeys with frontal lesions. *Neuropsychologia*, **14**, 481–490.

BONIN, G. VON and BAILEY, P. (1947) *The Neocortex of Macaca Mulatta*. Illinois Monographs in the Medical Sciences. Chicago: University of Illinois Press.

BRODY, B. A., UNGERLEIDER, L. G. and PRIBRAM, K. H. (1977) The effects of instability of the visual display on pattern discrimination learning by monkeys: Dissociation produced after resections of frontal and inferotemporal cortex. *Neuropsychologia*, **15**, 439–448.

BUTTER, C. (1969) Perseveration in extinction and discrimination reversal tasks following selective frontal ablations in *Macaca Mulatta*. *Physiology and Behaviour*, **4**, 163–171.

BUTTERS, N. and BARTON, M. (1970) Effects of parietal lobe damage on the performance of reversible operations in space. *Neuropsychologia*, **8**, 205–214.

—— —— and BRODY, B. A. (1970) Role of the right parietal lobe in the mediation of cross-modal associations and reversible operations in space. *Cortex*, **6**, 174–190.

—— SOELDNER, C. and FEDIO, P. (1972) Comparison of parietal and frontal lobe spatial deficits in man: Extrapersonal vs. personal (egocentric) space. *Perceptual and Motor Skills*, **34**, 27–34.

CRITCHLEY, M. (1953) *The Parietal Lobes*. New York: Hafner Publishing Co.

FUSTER, J. M. (1973) Unit activity in prefrontal cortex during delayed-response performance: Neuronal correlates of transient memory. *Journal of Neurophysiology*, **36**, 61–78.

GERSTMANN, J. (1940) Syndrome of finger agnosia, disorientation for right and left, agraphia and acalculia. *Archives of Neurology and Psychiatry, Chicago*, **44**, 398–407.

GOLDMAN, P. S. and ROSVOLD, H. E. (1970) Localization of function within the dorsolateral prefrontal cortex of the rhesus monkey. *Experimental Neurology*, **27**, 291–304.

—— —— VEST, B. and GALKIN, T. W. (1971) Analysis of the delayed-alternation deficit produced by dorsolateral prefrontal lesions in the rhesus monkey. *Journal of Comparative and Physiological Psychology*, **77**, 212–220.

GRUENINGER, W. E. and PRIBRAM, K. H. (1969) Effects of spatial and nonspatial distractors on performance latency of monkeys with frontal lesions. *Journal of Comparative and Physiological Psychology*, **68**, 203–209.

HYVÄRINEN, J. and PORANEN, A. (1974) Function of the parietal associative area 7 as revealed from cellular discharges in alert monkeys. *Brain*, **97**, 673–692.

IVERSEN, S. D. and MISHKIN, M. (1970) Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research*, **11**, 376–386.

JACOBSEN, C. F. (1936) Studies of cerebral functions in primates. I. The function of the frontal association areas in monkeys. *Comparative Psychology Monographs*, **13**, 1–60.

—— and NISSEN, H. W. (1937) Studies of cerebral function in primates. IV. The effects of frontal lobe lesions on the delayed alternation habit in monkeys. *Journal of Comparative Psychology*, **23**, 101–112.

KENNARD, M. A. (1939) Alterations in response to visual stimuli following lesions of frontal lobe in monkeys. *Archives of Neurology and Psychiatry, Chicago*, **41**, 1153–1165.

KIMBLE, D. P. and PRIBRAM, K. H. (1963) Hippocampectomy and behavior sequences. *Science*, **139**, 824–825.

KUBOTA, K. and NIKI, H. (1971) Prefrontal cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology*, **34**, 337–347.

LURIA, A. R. (1966) *Human Brain and Psychological Processes.* (Translated by Basil Haigh). New York: Harper and Row.

—— PRIBRAM, K. H. and HOMSKAYA, E. D. (1964) An experimental analysis of the behavioral disturbance produced by a left frontal arachnoidal endothelioma (meningioma). *Neuropsychologia*, **2**, 257-280.

MILNER, B. (1963) Effects of different brain lesions on card sorting: The role of the frontal lobes. *Archives of Neurology, Chicago*, **9**, 99-100.

—— (1964) Some effects of frontal lobectomy in man. In: *The Frontal Granular Cortex and Behavior.* Edited by J. M. Warren and K. Akert. New York: McGraw Hill, pp. 313-334.

—— (1971) Interhemispheric differences and psychological processes in man. *British Medical Bulletin*, **27**, 272-277.

MISHKIN, M. (1964) Perseveration of central sets after frontal lesions in monkeys. In: *The Frontal Granular Cortex and Behavior.* Edited by B. M. Warren and K. Akert. New York: McGraw-Hill, pp. 219-241.

—— and PRIBRAM, K. H. (1955) Analysis of the effects of frontal lesions in monkey. I. Variations of delayed alternation. *Journal of Comparative and Physiological Psychology*, **48**, 492-495.

—— —— (1956) Analysis of the effects of frontal lesions in monkey. II. Variations of delayed response. *Journal of Comparative and Physiological Psychology*, **49**, 36-40.

—— VEST, B., WAXLER, M. and ROSVOLD, H. E. (1969) A re-examination of the effects of frontal lesions on object alternation. *Neuropsychologia*, **7**, 357-363.

MOUNTCASTLE, V. B., LYNCH, J. C., GEORGOPOULOS, A., SAKATA, H. and ACUNA, C. (1975) Posterior parietal association cortex of the monkey: Command functions for operations within extrapersonal space. *Journal of Neurophysiology*, **38**, 871-908.

—— PASSINGHAM, R. E. (1972) Non-reversal shifts after selective prefrontal ablations in monkeys (*Macaca mulatta*). *Neuropsychologia*, **10**, 41-46.

PINTO-HAMUY, T. and LINCK, P. (1965) Effect of frontal lesions on performance of sequential tasks by monkeys. *Experimental Neurology*, **12**, 96-107.

POHL, W. (1973) Dissociation of spatial discrimination deficits following frontal and parietal lesions in monkeys. *Journal of Comparative and Physiological Psychology*, **82**, 227-239.

—— POPPEN, R. L., PRIBRAM, K. H. and ROBINSON, R. S. (1965) Effects of frontal lobotomy in man on the performance of a multiple choice task. *Experimental Neurology*, **11**, 217-229.

PRIBRAM, K. H. (1955) Lesions of 'frontal eye fields' and delayed response of baboons. *Journal of Neurophysiology*, **18**, 105-112.

—— (1958) Comparative neurology and the evolution of behavior. In: *Behavior and Evolution.* Edited by A. Roe and G. G. Simpson. New Haven: Yale University Press, pp. 140-164.

—— (1961) A further experimental analysis of the behavioral deficit that follows injury to the primate frontal cortex. *Experimental Neurology*, **3**, 432-466.

—— (1969) DADTA III: An on-line computerized system for the experimental analysis of behavior. *Perceptual and Motor Skills*, **29**, 599-608.

—— AHUMADA, A., HARTOG, J. and ROSS, L. (1964) A progress report on the neurological processes disturbed by frontal lesions in primates. In: *The Frontal Granular Cortex and Behavior.* Edited by J. M. Warren and K. Akert. New York: McGraw-Hill, pp. 28-55.

PRIBRAM, K. H., CHOW, K. L. and SEMMES, J. (1953) Limit and organization of the cortical projection from the medial thalamic nucleus in monkey. *Journal of Comparative Neurology*, **98**, 433–448.

—— and MISHKIN, M. (1956) Analysis of the effects of frontal lesions in monkey. III. Object alternation. *Journal of Comparative and Physiological Psychology*, **49**, 41–45.

—— PLOTKIN, H. C., ANDERSON, R. M. and LEONG, D. (1977) Information sources in the delayed alternation task for normal and 'frontal' monkeys. *Neuropsychologia*, **15**, 329–340.

—— and TUBBS, W. E. (1967) Short-term memory, parsing, and the primate frontal cortex. *Science*, **156**, 1765–1767.

SEMMES, J., WEINSTEIN, S., GHENT, L. and TEUBER, H. L. (1963) Correlates of impaired orientation in personal and extrapersonal space. *Brain*, **86**, 747–772.

SIEGEL, S. (1956) *Nonparametric Statistics for the Behavioral Sciences.* New York: McGraw-Hill.

STAMM, J. S. and ROSEN, S. C. (1969) Electrical stimulation and steady potential shifts in prefrontal cortex during delayed response performance by monkeys *Acta Neurobiologiae Experimentalis, Warszawa*, **29**, 385–399.

TEUBER, H. L. (1964) The riddle of frontal lobe function in man. In: *The Frontal Granular Cortex and Behavior*. Edited by J. M. Warren and K. Akert. New York: McGraw-Hill, pp. 410–444.

—— and MISHKIN, M. (1954) Judgment of visual and postural vertical after brain injury. *Journal of Psychology*, **38**, 161–175.

UNGERLEIDER, L. G. and BRODY, B. A. (1977) Extrapersonal spatial orientation. The role of posterior parietal, anterior frontal and inferotemporal cortex. *Experimental Neurology*, **56**, 265–280.

(*Received July 7, 1977*)

Brain (1978), **101**, 635–648

LONG LATENCY EVENT-RELATED COMPONENTS OF THE AUDITORY EVOKED POTENTIAL IN DEMENTIA

by DOUGLAS S. GOODIN, KENNETH C. SQUIRES *and* ARNOLD STARR

(*From the Department of Neurology, University of California, Irvine, 101 City Drive South, Orange, California 92668*)

INTRODUCTION

EVOKED potentials are now used as an objective test of afferent function in patients with neurological and sensory disorders (Starr, 1978). The testing of the optic nerves in multiple sclerosis (Feinsod, Abramsky and Auerbach, 1973; Halliday, McDonald and Mushin, 1972; Namerow and Enns, 1972; Richey, Kooi and Tourtellotte, 1971), the evaluation of hearing in infants and retarded individuals (Galambos and Hecox, 1977; Rapin and Schimmel, 1977; Starr, Amlie, Martin and Sanders, 1977), and the definition and location of brain-stem lesions (Starr and Hamilton, 1976; Stockard and Rossiter, 1977) are particular examples of successful application of evoked potential measures to neurological disease.

There is also a need in neurology for an objective measure of the physiological state of those areas of the brain which are involved in perception and cognition. The presence of normal, or near normal, sensory evoked potentials does not guarantee that sensory information is actually utilized. For example, perfectly normal auditory brain-stem potentials may be recorded from comatosed patients who are not responsive to acoustic stimuli (Starr and Achor, 1975) and visually evoked cortical potentials have been recorded from individuals who were behaviourally blind (Bodis-Wollner, Atkin, Raab and Wolkstein, 1977). Thus, even though evoked potentials may indicate that an afferent system is intact, a deficit in other neural structures can render the input functionally useless.

There are certain components of the evoked potential, however, that seem to be associated with cognitive processes. Evoked potentials may be separated into two sets of components; 'stimulus-related' components that are sensitive to the physical characteristics of the stimulus, and 'event-related' components that are dependent on the information content of the stimulus (Sutton, Braren, Zubin and John, 1965). Event-related potentials appear only when a subject 'attends' to stimuli, and then only when a stimulus has meaning for the subject. They may also appear in the absence of stimulus-related potentials when the eliciting event is the omission of an expected stimulus (Weinberg, Walter and Crow, 1970; Picton and Hillyard, 1974).

The event-related potentials have relatively long latencies (greater than 150 ms) and are of largest amplitude at the midline overlying the parietal lobes and posterior frontal lobes (Picton and Hillyard, 1974; Simson, Vaughan and Ritter, 1977), structures which have traditionally been considered as being involved in cognition. The stimulus-related potentials, on the other hand, occur at shorter latencies (less than 180 ms) and include the far-field reflection of events rising from sensory pathways within the brain-stem and spinal cord (Cracco and Cracco, 1976; Jewett and Williston, 1971; Wiederholt and Iraqui-Madoz, 1977) and cortical potentials distributed for the most part over the primary sensory regions (for example, over the occipital lobes for visual stimuli, over the central regions for somatosensory and acoustic stimuli, Goff, Allison and Vaughan, 1978).

The most prominent of the event-related potentials is the P3 component, a positive wave occurring at a latency of 300 to 500 ms. Many studies with normal subjects have linked the P3 component to processes involved in perception and cognition (*see* Tueting, 1978, or Donchin, Ritter and McCallum, 1978, for a review). In particular, the latency of the P3 component is closely correlated with the latency of decision processes, when such latencies are measured by behavioural reaction time (Kutas, McCarthy and Donchin, 1977; Ritter, Simson and Vaughan, 1972; Roth, Ford and Kopell, 1978; Squires, Donchin, Squires and Grossberg, 1977). Thus, any factor which modifies the timing of neural mechanisms underlying perception and cognition may conceivably be reflected in changes in the latency of the P3 component. It was our hypothesis that neurological disorders characterized by altered mental functions might be associated with an alteration in the P3 component.

Dementia is a cardinal example of disordered cognitive function. The affected individual has deficits in attention, memory and the processing of sensory input. This study was conducted to determine whether patients with dementia would show alterations in the P3 component. Fifty-three patients were tested. Twenty-seven of the patients were demented, and the other 26 had normal mental functions. The evoked potentials from these patients were compared with data collected previously from 40 normal adult subjects ranging in age from 15 to 76 years (Goodin, Squires, Henderson and Starr, 1978).

METHODS

Subjects

The first group of patients consisted of 16 females and 11 males, ranging in age from 25 to 80 years, who were diagnosed as demented by clinical neurological assessment. The ætiologies of their disorders were established by appropriate laboratory procedures. Their mental function was quantified in our laboratory by the Mini-mental Status examination (Folstein, Folstein and McHugh, 1975) and a mark of 25 or less out of a possible 30 points was used to define dementia. Normal subjects with no known disease usually scored either 29 or 30 points on this test. The range of scores for the demented group was 12 to 25, with a mean of 20·7 (±3·8). The diagnoses and mean mental status examination scores for this group are shown in Table 1.

TABLE 1. DIAGNOSES AND MENTAL-STATUS EXAMINATION SCORES OF THE DEMENTED PATIENTS

	No.	*MMS**
Presenile dementia	9	20·8**
Metabolic encephalopathy***	5	21·0
Hydrocephalus	5	20·6
Cerebrovascular disease	2	21·5
Brain tumour	1	17·0
Uncertain ætiology	5	21·8
Mean	27	20·7

* Mini-mental Status score (MMS) based on test of Folstein *et al.* (1975). ** One patient could not be tested and is not included in the calculations. *** Hypothyroidism, alcoholic with severe electrolyte disturbances, anoxia (2), steroid encephalopathy.

The second group of patients consisted of 12 females and 14 males ranging in age from 19 to 78 years. None was considered by the neurologists to have any deficit in mental function. The scores on the mental status examination for this group ranged from 27 to 30, with a mean of 28·8 (±0·84). The diagnoses and mean mental status examination scores for this group are shown in Table 2.

TABLE 2. DIAGNOSES AND MENTAL-STATUS EXAMINATION SCORES OF THE NON-DEMENTED PATIENTS

	No.	*MMS**
Multiple sclerosis	4	29·0
Depression	4	28·5
Cerebrovascular disease	3	28·7
Parkinson's disease	3	29·3
Schizophrenia	2	27·5
Hydrocephalus	1	29·0
Porencephalic cyst	1	30·0
Miscellaneous**	8	29·8
Mean	26	28·8

* Mini-mental Status score (MMS) based on test of Folstein *et al.* (1975). ** Diabetic neuropathy, causalgia, bilateral subdural hæmatoma, diffuse cortical atrophy, anosmia with left arm weakness, gait apraxia (2), vertigo.

Procedure

It was important to develop a procedure which could be used in a clinical electrodiagnostics laboratory. Consequently, the procedure had to be designed such that it could be completed in a single short-duration testing session; the equipment required for stimulus generation and evoked potential recording had to be kept at a minimum, the behavioural task had to be simple and not require any preliminary training, and finally, the evoked potential results had to be easily quantified.

An audio tape was prepared containing four hundred tone bursts (50 ms in duration with 10 ms rise/fall times and an intensity of 55 dB SL). The tones were presented binaurally through earphones at a rate of one every 1·5 s. Eighty-five per cent of the tones had a frequency of 1000 Hz and 15 per cent a frequency of 2000 Hz. The stimulus sequence was random with the constraint that no two rare (2000 Hz) tones appeared in succession.

Each patient was first presented with a portion of the tape containing the tone sequence. The patient was then questioned about what was heard. Testing was continued if the patient was able to clearly hear the tones and distinguish between the two pitches.

The patients were then instructed to count and keep a mental record of the number of rare tones in the sequence and to report the total at the end of the run. They were also cautioned to refrain from moving their eyes and to avoid movements associated with counting. Normally the sequence was presented twice to each patient. The total testing procedure was usually completed in thirty minutes.

Silver disc electrodes were affixed to the scalp at F_z, C_z and P_z with collodion and referred to linked mastoids. Additional electrodes were positioned superior and lateral to the right eye in order to monitor eye-related potentials. The electroencephalogram was amplified 10,000 times with a bandpass of 0·3 to 70 Hz. The evoked potential waveforms were averaged separately for the rare and frequent tones for 768 ms (6 ms per point) following the onset of tone.

The amplitudes and latencies of the various peaks of the averaged evoked potentials were measured from x–y plots of the waveforms. Peak latencies and amplitudes of the stimulus-related N1 and P2 components of the evoked potentials were obtained from the evoked potentials for the frequent (1000 Hz) tone. The amplitude of the stimulus-related potential was taken as the voltage difference between the N1 and P2 peaks. The peak latency for the P3 component was obtained from the potentials evoked by the rare (2000 Hz) tone by extrapolating lines from the leading and trailing slopes of the peak and measuring the latency at the intersection of the lines. The amplitude of the P3 component was taken at the most positive point of the peak, regardless of whether it matched the latency derived from extrapolation, and was measured with respect to a baseline voltage over the first 50 ms of the waveform. The bandpass of the recording system effectively attenuated the brain-stem and middle-latency potentials that occur in this time period (Picton, Hillyard, Krausz and Galambos, 1974), making this portion of the waveform flat. All latency and amplitude measures were derived from the C_z waveform; the waveforms for the other two electrode sites were however used to help define the components.

RESULTS

Task Performance

Normal subjects had no trouble performing the task. In virtually every case their count was within two or three of the actual number of rare-tone presentations. The neurological patients who were not demented were also able to perform the task satisfactorily. They were, however, susceptible to losing count and their tallies were more variable than for the normal subjects. Many of the demented patients were also able to perform the task, though their counts were widely variable. When patients were apparently unable to carry out the task or to maintain their attention to the tonal stimuli, frequent reminders to listen for the 'different' tones were given by one of the examiners. These reminders were adequate since the patients were co-operative and highly motivated to please the examiners, even though they sometimes had difficulty remembering the task.

Evoked Potentials

(1) *Normal subjects.* Evoked potential waveforms recorded from the vertex (C_z) for a normal subject are shown in fig. 1. The waveform for the frequent tone shows the characteristic negative (N1) and positive (P2) components of the auditory 'vertex potential' (Davis and Zerlin, 1966) with latencies of about 100 and 200 ms, respectively. These components are considered to be stimulus-related since they are elicited by both rare and frequent tones. The evoked potential for the rare tone, however, was quite different, being characterized not only by the stimulus-related components but also by a large event-related positive component labelled P3.

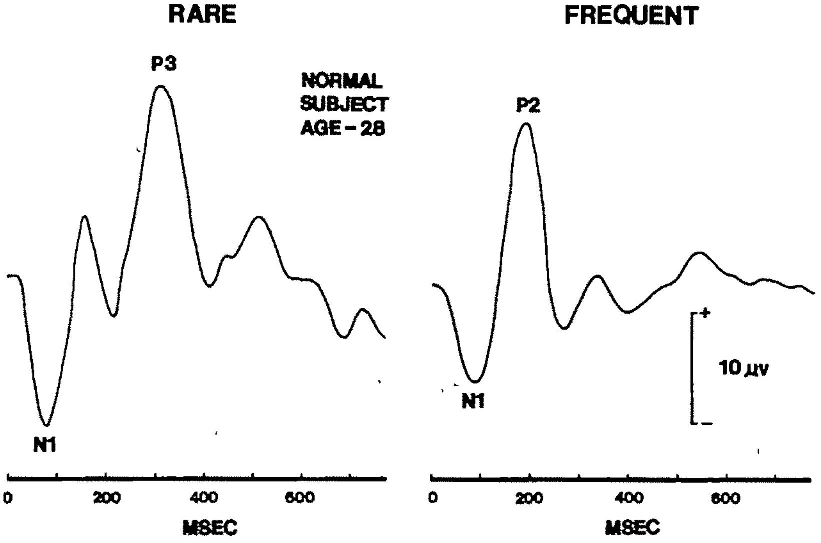


FIG. 1. Evoked potential waveforms recorded between the vertex (C_z) and linked mastoids for a normal subject. The potential evoked by the rare tone is on the left and the potential evoked by the frequent tone is on the right. In these and all subsequent figures positive voltage at the vertex is plotted upwards.

In a previous report we described changes in the amplitudes and latencies of the evoked potential components in normal subjects as function of age using this experimental procedure (Goodin *et al.*, 1978). The results of a standard regression analysis, in which the best-fit straight line was derived to describe the changes in each component as a function of age, are summarized in Table 3. The resulting regression equations for each component (defined by the slope as a function of age and the intercept value at age 15 years) indicated that, in general, the evoked potential components both shifted to longer latencies and decreased in amplitude with increasing age. This was most striking for the P3 component. A calculation of the expected change in P3 latency between ages 15 and 75 from the regression equation revealed an increase of nearly 100 ms (from 310 ms at age 15 to 408 ms at age 75). A similar calculation for the P3 amplitude yielded a decrease of about 11 μv (from 14·9 μv to 4·1 μv) over that age range. Smaller amplitude and/or latency changes were seen for the stimulus-related components.

TABLE 3. AGE-RELATED VARIATIONS IN THE AMPLITUDES AND LATENCIES OF AUDITORY EVOKED POTENTIAL COMPONENTS FOR NORMAL SUBJECTS AGED 15 TO 76 YEARS

	Slope	*Correlation coefficient*	*Standard error about regression line*	*Value at age 15 yrs*	*Significance*
N1 latency	0·13 ms/yr	0·228	8 ms	94 ms	—*
P2 latency	0·74 ms/yr	0·560	19 ms	168 ms	$P<0{\cdot}001$
P3 latency	1·64 ms/yr	0·810	21 ms	310 ms	$P<0{\cdot}001$
N1–P2 amplitude	$-0{\cdot}15\ \mu v$/yr	$-0{\cdot}420$	$5{\cdot}56\ \mu v$	$15{\cdot}6\ \mu v$	$P<0{\cdot}01$
P3 amplitude	$-0{\cdot}18\ \mu v$/yr	$-0{\cdot}476$	$5{\cdot}84\ \mu v$	$14{\cdot}9\ \mu v$	$P<0{\cdot}005$

* Non-significant

(2) *Patients.* Evoked potential waveforms (C_z) for one normal subject, one neurological patient without dementia and one demented patient are shown in fig. 2. Because of the effect of age on the evoked potential components, three individuals of approximately the same age were selected for the figure. The peak latencies for the normal subject are indicated by the dashed lines. A comparison of the waveform peaks for the two patients with the dashed lines illustrates the principle findings of this study. The latency of the P3 component for the demented patient (Mini-mental Status score 22) was 50 ms greater than for the normal subject, while the latency for the non-demented neurological patient (Mini-mental Status score 29) was nearly the same as for the normal subject (10 ms earlier).

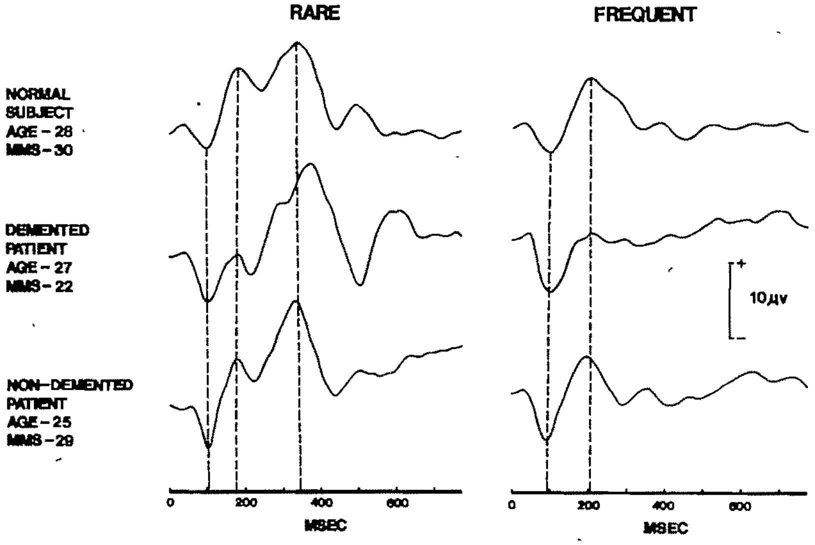


FIG. 2. Evoked potential waveforms for the rare and frequent tones recorded between the vertex (C_z) and linked mastoids for a normal subject (*top*), a demented patient (*middle*) and a non-demented patient (*bottom*). MMS = Mini-mental Status score (*see* Table 1).

The P3 latencies for the normal subjects and the patients are plotted as a function of age in fig. 3. The upper panel shows the results for the normal subjects with the calculated regression line and the lines indicating one and two standard deviations (σ) superimposed. In the middle and bottom panels the results for the demented and non-demented patients, respectively, are plotted with the regression and standard deviation lines for the normal subjects superimposed.

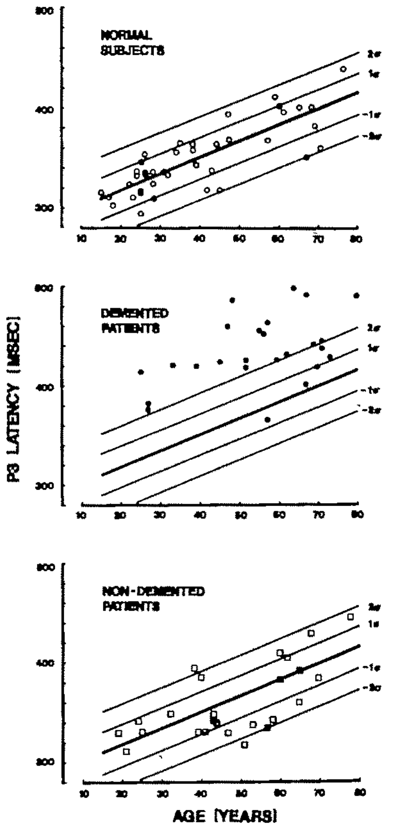


FIG. 3 The latencies of the P3 component are plotted as a function of age for normal subjects (*top*), demented patients (*middle*) and a non-demented patients (*bottom*).

Of the 53 patients tested, a reliable measure of the P3 latency could not be made in just 3 cases; 2 demented patients and one non-demented patient. One of the patients (demented) would not be still during the test and the waveforms were contaminated by muscle artifact. For the other 2 patients, the evoked potentials consisted of the N1 and P2 components followed by a broad positivity between 300 and 500 ms without any clear peak.

It is clear from fig. 3 that the P3 latencies for patients with dementia generally exceed the normative values for each patient's age. Only one demented patient had a P3 latency which was shorter than the norm and 80 per cent had a P3 latency which exceeded the norm by two or more standard deviations. The distribution of the P3 latencies for the patients without dementia was essentially identical to that for the normal subjects.

TABLE 4. DEVIATIONS FROM NORMAL OF THE AMPLITUDES AND LATENCIES OF AUDITORY EVOKED POTENTIAL COMPONENTS FOR DEMENTED AND NON-DEMENTED PATIENTS

		Mean deviation from normal (σ)	$t(df=62)$	*Significance*
N1 latency	Dementia	0·50±1·46	1·58	—*
	Non-dementia	0·39±1·00	1·49	—
P2 latency	Dementia	−1·10±1·3	0·36	—
	Non-dementia	0·46±1·2	1·69	—
P3 latency	Dementia	2·83±1·5	8·88	$P<0{\cdot}001$
	Non-dementia	0·11±1·3	0·20	—
N1–P2 amplitude	Dementia	−0·24±1·50	0·99	—
	Non-dementia	0·36±1·30	1·26	—
P3 amplitude	Dementia	−0·60±0·97	2·31	$P<0{\cdot}05$
	Non-dementia	0·23±1·19	0·82	—

* Non-significant.

Table 4 presents an analysis of the amplitudes and latencies of the various evoked potential components for the two groups of patients compared to normal values for each patient's age. The values are expressed in terms of their deviation from the appropriate regression line for normal subjects. For example, the P3 latency deviation for each patient was obtained by subtracting the expected P3 latency for the patient's age from the actual latency, and the difference was divided by the standard deviation about the normal regression line (for the P3 latency this was 21 ms, *see* Table 3). This procedure converts the data to a form where direct comparisons with normal can be made regardless of age. The magnitude of any deviation can also be interpreted on a statistical basis in terms of the probability that it is within a defined normal range.

The non-demented patients did not differ significantly from normal for any of the amplitude or latency measures. The demented patients also did not differ significantly from normal in terms of their N1 and P2 components. However, the latency of the P3 component for the demented patients was significantly greater than normal, and the amplitude of the P3 component was significantly smaller than normal.

A breakdown of the mean P3 latency deviations from normal for the various subgroups of patients is presented in Table 5. These results demonstrate the consistency of the latency effect within the various diagnostic categories.

TABLE 5. MEAN DEVIATION FROM NORMAL IN P3 LATENCY FOR PATIENTS

Demented patients	Δ *P3 latency* (σ)
Presenile dementia	+2·30*
Metabolic encephalopathy	+3·87*
Hydrocephalus	+2·32
Cerebrovascular disease	+3·06
Brain tumour	+4·00
Uncertain ætiology	+3·51
Mean	+2·93
Non-demented patients	
Multiple sclerosis	+0·32
Depression	−0·54
Cerebrovascular disease	−0·26
Parkinson's disease	+0·94
Schizophrenia	+0·90
Hydrocephalus	−0·93
Porencephalic cyst	+0·83
Miscellaneous	−0·15*
Mean	−0·02

* One patient could not be assigned a P3 latency and is not included in the computation

DISCUSSION

This study demonstrates that impaired mental functioning in dementia is highly correlated with changes in the latency and amplitude of the P3 component of the auditory evoked cortical potential. As a group, the patients with dementia had P3 components which were both delayed in latency and smaller in amplitude than normal. These changes in the P3 component cannot be attributed to the presence of a nervous system disease *per se* or to being in hospital. This is demonstrated by the results from the control group of non-demented patients, which were within the normal range. The P3 changes apparently stem from the underlying dementia regardless of the ætiology (*see* Table 5).

The magnitude of the P3 latency increase with dementia was, on the average, 2·93 standard deviation units from normal, and reliably separated the patients with dementia from both normal subjects and from neurological patients with normal mental function. Twenty of the 25 demented patients who had identifiable P3 components had a P3 latency which exceeded the normal value for the patient's age by more than two standard deviations. For 12 of the demented patients the latency difference exceeded three standard deviations. In contrast, only one non-demented patient had a P3 latency that exceeded the predicted value by more than two standard deviations, which would be expected merely on statistical grounds. Thus, if a P3 latency which exceeds normal by two standard deviations is adopted as the criterion for electrophysiologically defining dementia, a rate of 5 per cent false positives would be expected while 80 per cent of the patients with dementia would be correctly classified. This suggests that the P3 latency can provide a sensitive and perhaps specific test for dementia. Such a test would be extremely useful in distinguishing dementia from psychiatric disorders such as depression or schizophrenia which may be accompanied by an apparent, but not actual, deterioration in mental function. Four patients with depression and 2 with schizophrenia were tested here and all had normal latency P3 components. Clearly, however, a more extensive investigation of the effects of psychiatric illness on the P3 component is required before the reliability of this distinction between psychosis and dementia can be fully documented.

The amplitude of the P3 component also changed (decreased) in dementia, but the magnitude of the change was small relative to the normal variation in the measure (0·60 σ, Table 4). Thus, it is unlikely that the P3 amplitude alone can provide a measure of mental function which is adequate for assessing individual patients.

This procedure seems eminently suitable for the testing of patients. Of the 53 patients examined, only 3 did not have a reliable P3 component. We did not, however, test patients who were unco-operative or who had gross involuntary movements which might have interfered with the recordings.

It is unclear to what extent the task of counting the rare tones is itself involved in eliciting the P3 component. Several of the demented patients probably did not understand the task. Clear P3 components, however, were present for the rare tones but not the frequent ones, even for those patients. From an operational standpoint it would appear then that the sequence of tones itself is in some instances sufficient to induce the differential cognitive processing of the rare and frequent tones. Similar results have been reported for normal subjects (Ritter *et al.*, 1968; Roth, 1973).

While patients with dementia showed changes in the P3 component of the cortical potential, there were no significant effects on the earlier stimulus-related components, N1 and P2. In a previous study of visual evoked potentials, Visser, Stam, Van Tilburg, Op Den Velde, Blom and De Rijke (1976) reported significant latency changes for peaks corresponding to the stimulus-related components. The differences between their results and those reported here may be either due to a modality difference or to the fact that they failed to compensate for age differences between their normal subjects and their demented patients, which can affect visual evoked potential latencies (Celesia and Daly, 1977).

The cognitive changes associated with senescence and dementia may be distinguished on the basis of differential effects on the various components of the evoked potential. The normal aging process is associated with a significant effect on the latency of both the P2 and P3 components, though the former change is smaller than that for the P3. However, if in dementia P2 and P3 changes occurred in the same ratio as they did for normal aging, the P2 latency change would have amounted to approximately 25 ms. The lack of any significant change in the P2 component other than that associated with aging clearly distinguishes the physiological processes affecting evoked potentials in aging and dementia. This is particularly relevant in the case of presenile dementia which has been suggested to be due to an accelerated aging process (Terry, 1976). For the senile patients tested here, there was a clearly significant change in the mean P3 latency (2·30 σ, 48 ms) without a concomitant change in P2 latency ($-0{\cdot}16\ \sigma$, -3 ms).

One possible explanation for the increase in P3 latency found in dementia is that the demented patients were slow in identifying and processing the stimuli relative to the normal subjects or non-demented patients. In normal subjects, increases in both task difficulty (Ritter *et al.*, 1972; Squires *et al.*, 1977) and task complexity (Kutas *et al.*, 1977) prolong the P3 latency, presumably because the decision processes involved take longer to complete. The increased decision latencies can also be inferred from behavioural reaction times (c.f. Squires *et al.*, 1977). In such situations proportional changes in the latencies of the stimulus related components are not found (Ritter *et al.*, 1972). Thus, there seems to be a parallel between the effects of dementia and the effects of increasing task difficulty in normal subjects on the latencies of the stimulus-related and event-related potentials. The possibility exists that in both instances the sequence of processes following the occurrence of the stimulus-related components, N1 and P2, require an increased amount of time and this is reflected in a change in the P3 latency.

In conclusion, the P3 latency appears to provide a measure for objectively defining dementia. As a clinical tool it is sensitive enough to differentiate a large proportion of demented patients from normal (nearly 80 per cent) with a low rate of false positives (5 per cent). In an electrodiagnostics laboratory the procedure can be readily implemented, it is applicable to most patients, and the resulting data can be easily analysed once normative data has been collected on a wide age range of normal subjects. These findings also raise the possibilities for experimental analysis of the cognitive factors contributing to the P3 component and their alterations following neurological lesions.

SUMMARY

Long-latency auditory evoked potentials were recorded from two groups of patients, with and without dementia, and were compared with those from a population of normal subjects ranging in age from 15 to 76 years. A sequence of tones of two different frequencies (1000 Hz and 2000 Hz) was presented and each patient was asked to count the occurrences of the rare ($P = 0{\cdot}15$) tones in the sequence. Evoked potential waveforms were averaged separately for the rare and frequent tone.

Of the various evoked potential components elicited by the tones, the P3 component (latency 300–500 ms) was found to be the most sensitive to aging in normal subjects. It was also the only component which could be used to differentiate between the demented patients and the normal subjects or non-demented patients.

The non-demented patients did not differ from normal in any waveform measure. The magnitude of the latency change of the P3 component in dementia relative to normal was sufficiently large that it may provide a practical and objective measure of dementia in a clinical setting.

ACKNOWLEDGEMENTS

The authors wish to thank Beverly Henderson for technical assistance in completing this study. This work was supported by USPHS Grant No. NS11876.

REFERENCES

BODIS-WOLLNER, I., ATKIN, A., RAAB, E. and WOLKSTEIN, M. (1977) Visual association cortex and vision in man: Pattern-evoked occipital potentials in a blind boy. *Science*, **198**, 629–631.

CELESIA, G. and DALY, R. (1977) Effects of ageing on visual evoked responses. *Archives of Neurology, Chicago*, **34**, 403–407.

CRACCO, R. and CRACCO, J. (1976) Somatosensory evoked potential in man. Far-field potentials. *Electroencephalography and Clinical Neurophysiology*, **41**, 460–466.

DAVIS, H. and ZERLIN, S. (1966) Acoustic relations of the human vertex potential. *Journal of the Acoustical Society of America*, **39**, 109–116.

DONCHIN, E., RITTER, W. and MCCALLUM, W. C. (1978) Cognitive psychophysiology. The endogenous components of the ERP. In: *Brain Event-Related Potentials in Man*. Edited by E. Callaway, P. Tueting and S. Koslow. New York: Academic Press. In press.

FEINSOD, M., ABRAMSKY, O. and AUERBACH, E. (1973) Electrophysiological examinations of the visual system in multiple sclerosis. *Journal of the Neurological Sciences*, **20**, 161–175.

FOLSTEIN, M., FOLSTEIN, S. and MCHUGH, P. (1975) 'Mini-mental State'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

GALAMBOS, R. and HECOX, K. (1977) Clinical applications of the brain-stem auditory evoked potentials. In: *Auditory Evoked Potentials in Man. Psychopharmacology Correlates of Evoked Potentials.* Edited by J. E. Desmedt. Basel: Karger, pp. 1–19.

GOFF, W., ALLISON, T. and VAUGHAN, JR., H. (1978) The functional neuroanatomy of event-related potentials. In: *Brain Event-Related Potentials in Man*. Edited by E. Callaway, P. Tueting and S. Koslow. New York: Academic Press. In press.

GOODIN, D., SQUIRES, K., HENDERSON, B. and STARR, A. (1978) Age-related variations in evoked potentials to auditory stimuli in normal human subjects. *Electroencephalography and Clinical Neurophysiology*, **44**, 447–458.

HALLIDAY, A. M., MCDONALD, W. I. and MUSHIN, J. (1972) Delayed visual evoked response in optic neuritis. *Lancet*, **i**, 982–985.

JEWETT, D. L. and WILLISTON, J. S. (1971) Auditory-evoked far fields averaged from the scalp of humans. *Brain*, **94**, 681–696.

KUTAS, M., MCCARTHY, G. and DONCHIN, E. (1977) Augmenting mental chronometry. The P300 as a measure of stimulus evaluation time. *Science*, **197**, 792–795.

NAMEROW, N. and ENNS, N. (1972) Visual evoked responses in patients with multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 829–833.

PICTON, T. and HILLYARD, S. (1974) Human auditory evoked potentials. II. Effects of attention *Electroencephalography and Clinical Neurophysiology*, **36**, 191–199.

—— —— KRAUSZ, H. and GALAMBOS, R. (1974) Human auditory evoked potentials. I. Evaluation of components. *Electroencephalography and Clinical Neurophysiology*, **36**, 179–190.

RAPIN, I. and SCHIMMEL, H. (1977) Assessment of auditory sensitivity in infants and in uncooperative handicapped children by using the late components of the average auditory evoked potential. In: *Auditory Evoked Potentials in Man, Psychopharmacology Correlates of Evoked Potentials.* Edited by J. E. Desmedt. Basel: Karger, pp. 79–92.

RICHEY, E., KOOI, K. and TOURTELLOTTE, W. (1971) Visually evoked responses in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 275–280.

RITTER, W., VAUGHAN JR., H. and COSTA, L. (1968) Orienting and habituation to auditory stimuli. A study of short term changes in average evoked response. *Electroencephalography and Clinical Neurophysiology*, **25**, 550–556.

—— SIMSON, R. and VAUGHAN JR., H. (1972) Association cortex potentials and reaction time in auditory discrimination. *Electroencephalography and Clinical Neurophysiology*, **33**, 547–555.

ROTH, W. (1973) Auditory evoked responses to unpredictable stimuli. *Psychophysiology*, **19**, 125–137.

—— FORD, J. and KOPELL, B. (1978) Long-latency evoked potentials and reaction time. *Psychophysiology*, **15**, 17–23.

SIMSON, R., VAUGHAN, JR., H. and RITTER, W. (1977) The scalp topography of potentials in auditory and visual discrimination tasks. *Electroencephalography and Clinical Neurophysiology*, **42**, 528–535.

SQUIRES, N., DONCHIN, E., SQUIRES, K. and GROSSBERG, S. (1977) Bisensory stimulation. Inferring decision-related processes from the P300 component. *Journal of Experimental Psychology: Human Perception and Performance*, **3**, 299–315.

STARR, A. (1978) Sensory evoked potentials in clinical disorders of the nervous system. *Annual Review of Neurosciences*, **1**, 103–127.

—— and ACHOR, L. J. (1975) Auditory brainstem response in neurological disease. *Archives of Neurology, Chicago*, **32**, 161–168.

—— AMLIE, R., MARTIN, W. and SANDERS, S. (1977) Development of auditory function in newborn infants revealed by auditory brainstem potentials. *Pediatrics*, **60**, 831–839.

—— and HAMILTON, A. (1976) Correlation between confirmed sites of neurological lesions and abnormalities of far-field auditory brainstem responses. *Electroencephalography and Clinical Neurophysiology*, **41**, 595–608.

STOCKARD, J. and ROSSITER, V. (1977) Clinical and pathologic correlates of brain stem auditory response abnormalities. *Neurology, Minneapolis*, **27**, 316–325.

SUTTON, S., BRAREN, M., ZUBIN, J. and JOHN, E. R. (1965) Evoked potential correlates of stimulus uncertainty. *Science*, **150**, 1187–1188.

TERRY, R. (1976) Dementia. A brief and selective review. *Archives of Neurology, Chicago*, **33**, 1–4.

TUETING, P. (1978) Event-related potentials, cognitive events and information processing. In: *New Perspectives in Event-Related Potential (ERP) Research*. Edited by D. Otto. Washington, D.C.: U.S. Government Printing Office. In press.

VISSIER, S., STAM, F., VAN TILBURG, W., OP DEN VELDE, W., BLOM, J. and DE RIJKE, W (1976) Visual evoked response in senile and presenile dementia. *Electroencephalography and Clinical Neurophysiology*, **40**, 385–392.

WEINBERG, H., WALTER, W G. and CROW, H. (1970) Intracerebral events in human related to real and imaginary stimuli. *Electroencephalography and Clinical Neurophysiology*, **29**, 1–9.

WIEDERHOLT, W. and IRAQUI-MADOZ, V. (1977) Far-field somatosensory potentials in the rat. *Electroencephalography and Clinical Neurophysiology*, **42**, 456–465.

(*Received March 21, 1978*)

Brain (1978), **101**, 649–659

SELECTIVE BLOCKADE BY SCOPOLAMINE OF SYNAPTIC RESPONSES IN CAT'S CAUDATE NUCLEUS AND ITS MODIFICATION BY LESIONS OF THE SUBSTANTIA NIGRA

by R. SPEHLMANN, K. NORCROSS *and* E. J. GRIMMER

(*From the Veterans Administration Lakeside Hospital and the Departments of Neurology and Pharmacology, Northwestern University Medical School, Chicago, Illinois 60611*)

INTRODUCTION

ACETYLCHOLINE (ACh) is commonly believed to be a synaptic transmitter in the caudate nucleus and to be involved in the pathophysiology of Parkinson's disease. However, the details of these roles of ACh remain unclear. The origin of nerve fibres releasing ACh in the caudate nucleus has not been clearly established. Most, if not all caudate neurons receive direct inputs (Kemp and Powell, 1971*b*) from the substantia nigra, thalamus, cortex and from the medium-sized (12–18 μ) neurons in the caudate nucleus itself which comprise over 95 per cent of neurons in this nucleus (Kemp and Powell, 1971*a*). ACh has been associated with different types of neuronal input. The existence of cholinergic interneurons is suggested by histochemical observations (Butcher and Bilezikjian, 1975; McGeer, McGeer, Grewaal and Singh, 1975). It has been proposed that ACh in the caudate nucleus is contained only in interneurons because lesions interrupting afferents from outside the caudate nucleus do not reduce the level of ACh (Butcher and Butcher, 1974; Fibiger and Grewaal, 1974), or the activity of choline acetylase or acetylcholinesterase (Kataoka, Bak, Hassler, Kim and Wagner, 1974; Lynch, Lucas and Deadwyler, 1972; McGeer, Fibiger, McGeer and Brooke, 1973; McGeer, McGeer, Fibiger and Wickson, 1971). This contrasts with the observation that stimulation of the nucleus ventralis anterior thalami increases the release of ACh from the caudate nucleus (McLennan, 1964) and has an effect on caudate neurons similar to that of micro-iontophoretic application of ACh (McLennan and York, 1966). However, ACh liberation in the caudate nucleus was also found to increase after stimulation of other structures including the substantia nigra and peripheral nerves (Portig and Vogt, 1969). Both findings could be due to secondary excitation of cholinergic interneurons.

In an attempt to determine if ACh is a transmitter of one of the major inputs to the neurons in the caudate nucleus, we investigated, in the first part of this study, the effects of ACh antagonists on the neuronal response to stimulation of these inputs reasoning that antagonists would block responses mediated by endogenous ACh. Because cholinergic receptors in the caudate nucleus have been found to be muscarinic (McLennan and York, 1966), we employed the muscarinic antagonists scopolamine and atropine. Scopolamine was used much more often as it was found to be less likely than atropine to produce local anæsthetic effects.

In the second part of this study, we attempted to determine the role of ACh in Parkinson's disease. This disease is thought to be due to the degeneration of dopamine-containing nigrostriatal connections which leads to striatal dopamine (DA) deficiency (Hornykiewicz, 1973) and to an apparent increase of cholinergic activity (Duvoisin, 1967; Van Woert, Ambani and Bowers, 1972). Such an imbalance (McGeer, Boulding, Gibson and Foulkes, 1961; Barbeau, 1962) could explain the beneficial effect of cholinolytics and the deleterious effect of the centrally acting anticholinesterase physostigmine on the manifestations of this disease (Duvoisin, 1967; Van Woert *et al.*, 1972). The increase of cholinergic activity is believed by some to be due to the loss of an inhibitory dopaminergic input to cholinergic neurons in the caudate nucleus (Stadler, Lloyd, Gadea-Ciria and Bartholini, 1973), but interruption of nigrostriatal connections produced no biochemical changes indicative of increased cholinergic activity: striatal acetylcholinesterase and choline acetylase levels were not altered during the first two (Kataoka *et al.*, 1974; Lynch *et al.*, 1972; McGeer *et al.*, 1971) or four (McGeer *et al.*, 1973) weeks after this lesion; the concentration of striatal ACh was found to be increased after diencephalic hemitransection in one study (Butcher and Butcher, 1974), but not in another one which used intranigral 6-hydroxydopamine injections (Fibiger and Grewaal, 1974). Simple interruption of inhibitory nigrostriatal input to a cholinergic system thus cannot explain an increase in cholinergic activity. A slow increase of this activity could be explained by the development of ACh supersensitivity (Duvoisin, 1967) or by the sprouting and regenerative overgrowth of cholinergic neurons in response to nigrostriatal degeneration (Spehlmann and Stahl, 1976).

In previous studies we found that neurons in the feline caudate nucleus depleted of DA by long-standing nigrostriatal lesions are excited by lower doses of ACh than are neurons in the intact caudate nucleus, suggesting that chronic DA depletion increases ACh sensitivity (Spehlmann, 1975). To determine whether this increased sensitivity to ACh may reflect an increased effectiveness of cholinergic transmission, we investigated, in the second part of this study, the effects of scopolamine on neuronal responses recorded in the caudate nucleus of cats with long-standing nigrostriatal lesions and compared them with those in cats without such lesions.

METHODS

Acute experiments were performed on 19 cats with and without lesions and 12 cats with lesions of the right nigrostriatal pathway; lesions were produced as previously described (Spehlmann, 1975). All animals were prepared as *encéphale isolé* and maintained on local anæsthesia to all contact and incision points. Heart rate, mean femoral arterial pressure, expired CO_2 concentration and body temperature were monitored. A craniotomy was made to expose the cortex overlying the head of the right caudate nucleus.

An 8-barreled micropipette was inserted into the caudate nucleus (A 16–18, L 2–5, D 5–7). Extracellular action potentials were recorded through the centre barrel which was filled with a 2 molar potassium citrate solution. Drug barrels contained scopolamine hydrobromide (1 M, pH 5·5), atropine sulphate (0 3 M, pH 7·3), acetylcholine chloride (1 M, pH 4), Na L-glutamate (2 M, pH 8) and GABA (4 M, pH 4). Drugs were ejected with currents of up to 2×10^{-7} A and retained with currents of up to 1×10^{-8} A of opposite polarity between ejections. All ejecting and retaining currents were returned through a barrel filled with NaCl (3 M, pH 7). This barrel was also used to pass currents of the same polarity and magnitude as used for drug iontophoresis to evaluate possible electrical effects. In animals without chronic lesions, bipolar stimulus electrodes were placed on the right side into the substantia nigra (A 3·5, L 4·5, D −4), nucleus ventralis anterior thalami (A 11, L 5, D 3·5), centrum medianum thalami (A 7, L 3, D 1), caudate nucleus (A 13, L 5, D 5) and anterior sigmoid gyrus (sensorimotor cortex). In animals with nigrostriatal lesions, stimulus electrodes were sometimes placed only in the caudate nucleus. After recording 16, 32 or 64 responses to each stimulus, scopolamine or atropine was applied and stimulation was repeated 30 s after the onset of micro-iontophoresis which continued during stimulation. Tape recordings of neuronal action potentials were used to plot post-stimulus histograms which were integrated to give the total number of action potentials before, during and after drug application.

At the end of each experiment, 100 mg of pentobarbital were given intravenously. Cats without lesions were perfused through the carotid arteries with formalin; locations of stimulus and recording electrodes were determined after fixation of the brain. In cats with lesions, both caudate nuclei were rapidly removed and stored at −80° C for later biochemical determinations of the levels of DA and norepinephrine (Chang, 1964) and of serotonin (Maickel, Cox, Saillant and Miller, 1968). The remaining parts of the brain were perfused by carotid injection of formalin and later sectioned for inspection of the lesions.

RESULTS

A. *The Non-dopamine-depleted Caudate Nucleus*

(1) *Neuronal responses to synaptic stimuli.* Most neurons did not fire spontaneously but responded to stimulation of one or more of the afferents. Stimulation of the caudate nucleus, sensorimotor cortex, nucleus ventralis anterior or centrum medianum thalami usually produced neuronal action potentials of all-or-none character beginning 7 to 10 ms after the stimulus and lasting 10 to 30 ms. In most neurons, the latency of the response to stimulation of the caudate nucleus was not clearly shorter than that of the responses to the other stimuli. Some neurons, however, responded to caudatal stimulation with discharges fired after only a few milliseconds. All of these responses were thought to be orthodromic because they varied slightly in latency and did not follow repetitive stimuli at rates of 100 per second or more. No definite antidromic responses were recorded. Stimulation of the substantia nigra elicited one or two discharges after 15 to 25 ms which had a sharp threshold, varied only slightly in latency and were also considered orthodromic.

(2) *Effect of scopolamine.* Scopolamine antagonized the response to caudate nucleus stimulation (fig. 1) in two-thirds of all neurons: in one-third, the number of

action potentials in 32 or 64 responses was reduced 20 to 50 per cent, in another one-third of the neurons, the response was reduced by over 50 per cent (Table 1). The effect of scopolamine on the responses to stimulation of the nucleus ventralis anterior and the centrum medianum thalami was similar to its effect on the response to stimulation of the caudate nucleus: neurons reacting to scopolamine with a block of responses to one of these stimuli showed a similar block of responses to the other stimuli at the same level of scopolamine application.

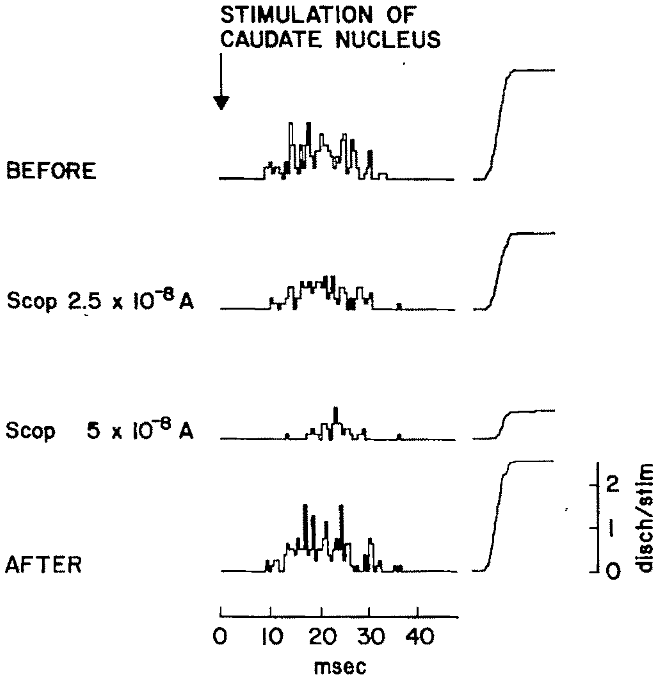


Fig. 1. The effect of scopolamine (Scop) iontophoresis on the responses to electrical stimulation of a neuron in the caudate nucleus near the recording site. Poststimulus histograms of action potentials fired during the first 50 ms after each of 32 stimuli to the caudate nucleus. Integrals of these histograms, calibrated in discharges per stimulus, are shown at the far right.

In contrast, the responses of the same neurons to stimulation of the sensorimotor cortex (fig. 2) and the substantia nigra were often not affected by scopolamine in doses which strongly depressed the response to stimulation of the caudate nucleus.

TABLE 1. EFFECTS OF SCOPOLAMINE ON NEURONAL RESPONSES TO DIFFERENT STIMULI

Responses to stimulation of:	*Total No. of neurons tested*	*Scopolamine block*		
		>50%	*20-50%*	*None*
Caudate nucleus	67	34%	33%	33%
Sensorimotor cortex	32	16%	13%	72%
Substantia nigra	37	14%	30%	57%

The incidence of a blocking effect of scopolamine on responses to stimulation of the sensorimotor cortex and the substantia nigra (Table 1) was significantly ($P < 0{\cdot}05$ in χ^2 tests) lower than the incidence of a blocking effect by scopolamine on the responses to stimulation of the caudate nucleus. In some neurons, scopolamine reduced the response to stimulation of either the sensorimotor cortex or the substantia nigra, but usually not as much as the response to stimulation of the caudate nucleus itself.

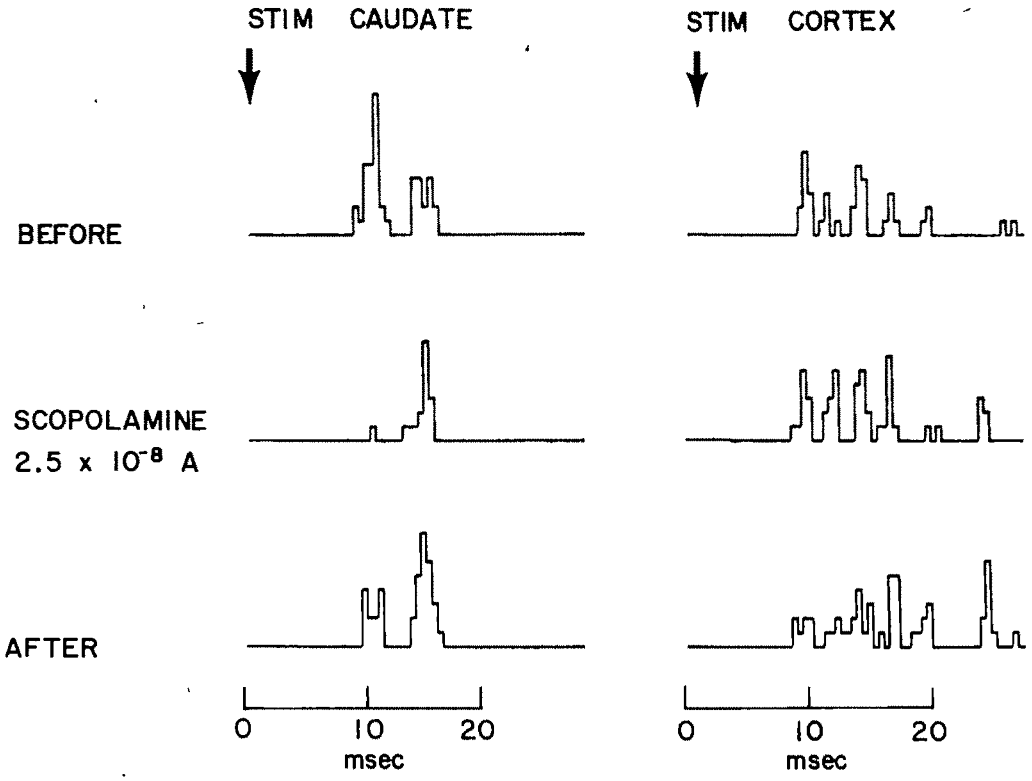


FIG. 2. Effect of scopolamine on the responses to stimulation of the caudate nucleus and of the sensorimotor cortex in a neuron in the caudate nucleus Histograms of action potentials fired after each of 32 stimuli.

This selective block of synaptic responses differed from a local anæsthetic effect obtained with scopolamine applications at intensities usually over 2×10^{-7} A and with atropine at even lower doses. Local anæsthetic effects were recognized by a decrease of amplitude and an increase of duration of action potentials and by the indiscriminate loss of firing in response to stimulation of all synaptic inputs and to L-glutamate iontophoresis. The selective blocking effect by scopolamine in low doses also contrasted with the general depressant action of GABA which abolished all responses without changing the shape of the action potentials. GABA given in addition to scopolamine promptly blocked scopolamine-resistant responses to stimulation of the sensorimotor cortex and scopolamine-resistant discharges of responses to stimulation of the caudate nucleus and of the thalamic inputs.

B. *The Dopamine-depleted Caudate Nucleus*

(1) *Amine levels.* The concentration of DA was 7·81±0·37 μg/g of wet weight (mean±SE) in the caudate nucleus of the unoperated side and 1·99±0·18 μg/g on the operated side. The reductions ranged from 62 to 94 per cent in different animals; the mean reduction was 30 per cent. Serotonin concentration was 0·93±0·02 μg/g on the unoperated side and 0·46±0·02 μg/g on the operated side; the mean reduction was 67 per cent Norepinephrine level amounted to 0·31±0·01 μg/g on the unoperated side and to 0·11±0·01 μg/g on the operated side; the mean reduction was 74 per cent. The differences of the mean concentrations on the two sides were significant for the three amines at $P < 0{\cdot}05$ in paired t-tests.

(2) *Neuronal responses to synaptic stimuli.* Stimulation of the caudate nucleus near the recording site, the thalamus and the cortex elicited neuronal responses in the DA-depleted caudate nucleus which were similar to those produced by similar stimuli in the intact caudate nucleus. Stimulation of the substantia nigra a few millimetres caudal to the nigrostriatal lesion rarely elicited responses in the caudate nucleus. When responses occurred, they consisted of 1 to 2 action potentials which appeared 15 to 25 ms after the stimulus. Because these responses did not differ from those recorded in the intact caudate nucleus, and because similar responses can be blocked by DA antagonists (Norcross and Spehlmann, 1978), they were thought to be mediated by uninterrupted nigrostriatal fibres.

(3) *Effect of scopolamine.* Scopolamine when applied with iontophoretic currents of up to 2×10^{-7} A reduced the responses to stimulation of the caudate nucleus by over 50 per cent in about one-half of 75 neurons, by 20 to 50 per cent in nearly one-third, and had no effect in the remainder. The incidence of these blocking effects in the DA-depleted caudate nucleus is higher than in the intact caudate nucleus, but the difference did not reach statistical significance.

Fig. 3 shows dose-response curves for the blocking effect of scopolamine, expressed as a percentage of control level of firing, versus the ejection current of

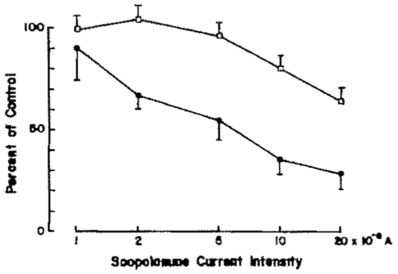


FIG. 3. The blocking effect of scopolamine on neuronal responses to caudate nucleus stimulation in the intact (□) and the dopamine-depleted (●) caudate nucleus Vertical bars indicate standard error of the mean.

scopolamine in 17 neurons in the DA-depleted caudate nucleus and in 23 neurons in the intact caudate nucleus. The control responses were very similar in the two groups of neurons; the average number of action potentials per stimulus, calculated from 32 or 64 responses of each neuron, was $2{\cdot}55 \pm 0{\cdot}97$ (mean ± SD) in the intact caudate nucleus and $2{\cdot}66 \pm 1{\cdot}68$ in the DA-depleted caudate nucleus. Scopolamine currents from 1 to 20×10^{-8} A produced a greater decrease of firing in the DA-depleted caudate nucleus than in the intact caudate nucleus. The differences in the mean decrease by scopolamine currents of 5, 10 and 20×10^{-8} A were statistically significant in t-tests ($P < 0{\cdot}01$). A complete block of the response was not achieved with the maximum current of 20×10^{-8} A used in this study.

DISCUSSION

The observation that scopolamine blocks the excitatory response of neurons in the caudate nucleus to stimulation near the recording site suggests that this response is in part mediated by cholinergic interneurons. A lesser reduction of responses to cortical and nigral stimulation, seen in some neurons, could be due to a scopolamine effect on secondarily activated cholinergic interneurons. The finding that responses to stimulation of the nucleus ventralis anterior and centrum medianum thalami were affected by scopolamine to the same degree as were responses to stimulation of the caudate nucleus may indicate that they were largely transmitted by recently described cholinergic fibres from the centrum medianum-parafascicular nucleus (Simke and Saelens, 1977) which pass through the nucleus ventralis anterior (Mehler, 1966), by cholinergic interneurons, or both. While direct cholinergic afferents from the nucleus ventralis anterior cannot be excluded, the failure of histological studies to demonstrate a direct projection (Carpenter, 1976; Jones and Leavitt, 1974) makes this possibility unlikely.

Although iontophoretic application of ACh was observed to cause a decrease of spontaneous firing in a proportion of neurons which varied in different studies (Bloom, Costa and Salmoiraghi, 1965; McLennan and York, 1966; Herz and Zieglgänsberger, 1968; Spehlmann, 1975; Zarzecki, Blake and Somjen, 1976), intracellular recordings showed that ACh has only a depolarizing effect on caudate neurons (Bernardi, Floris, Marciani, Morocutti and Stanzione, 1976). Inasmuch as scopolamine did not produce an increase of any of the synaptic responses, our results do not provide evidence for synaptically mediated cholinergic inhibition.

The observation that scopolamine often blocked only part of the response to stimulation of the caudate nucleus suggests that the scopolamine-resistant part was transmitted by noncholinergic interneurons or by noncholinergic fibres from afferents traversing the caudate nucleus near the stimulus electrode; the latter fibres probably contribute little if any to the response since it has been shown that complete deafferentation does not alter the response to stimulation of the caudate nucleus (Marco, Copack, Edelson and Gilman, 1973). A differential effect of scopolamine, presumably on postsynaptic ACh receptors, is supported by the finding that GABA, which had a strong depressant effect on all neurons tested, promptly and indiscriminately blocked all parts of the responses not blocked by scopolamine.

A comparison of the effect of scopolamine in the DA-depleted and non-depleted caudate nucleus showed that less scopolamine is needed to block neuronal responses to stimulation near the recording site in the DA-depleted caudate nucleus. This altered scopolamine effect is not likely to be the result of degenerative changes in the caudate nucleus altering the ability of scopolamine to diffuse through the tissue because nigrostriatal lesions of the type used in these experiments do not alter the neuronal sensitivity to L-glutamate (Spehlmann, 1975). The extent to which stimulus-liberated ACh contributed to the neuronal responses recorded in the caudate nucleus cannot be determined. Because micro-iontophoretic studies of the DA-depleted caudate nucleus had previously shown that less ACh is necessary for neuronal excitation (Spehlmann, 1975), and because our present findings show that less scopolamine is required to block neuronal excitation by presumably cholinergic interneurons, it seems that less endogenous ACh is required to transmit these synaptic responses in the DA-depleted caudate nucleus. Our results thus suggest that the effectiveness of cholinergic transmission by interneurons increases in the DA-depleted caudate nucleus. This increase could explain the increased effect of exogenous ACh seen in our previous experiments and it could also explain the mild but definite therapeutic effect of cholinolytics in Parkinson's disease.

SUMMARY

Because it is commonly believed that acetylcholine is a synaptic transmitter in the caudate nucleus and that the reduction of striatal biogenic amines in Parkinson's disease leads to acetylcholine supersensitivity in the caudate nucleus, we investigated the effects of the muscarinic blocking agent scopolamine on synaptic responses of neurons in the intact feline caudate nucleus and in the caudate nucleus depleted of dopamine by long-standing nigrostriatal lesions.

In the intact caudate nucleus, micro-iontophoretic application of scopolamine selectively blocked the neuronal responses to stimulation of the caudate nucleus near the recording site without affecting the responses to stimulation of the sensorimotor cortex or the substantia nigra in the same fashion. This suggests that acetylcholine is a synaptic transmitter of caudate interneurons. Responses to thalamic stimuli were also blocked by scopolamine, suggesting that acetylcholine may be a transmitter of thalamic afferents although the course of these afferents is unclear.

In the dopamine-depleted caudate nucleus scopolamine was more effective than in the intact caudate nucleus blocking the neuronal responses to stimulation of the caudate nucleus. This greater blocking effect by scopolamine suggests an increased

effect of endogenous acetylcholine in this response and supports previous observations of an increased excitatory effect of iontophoretic acetylcholine in the dopamine-depleted caudate nucleus. These results suggest that the acetylcholine supersensitivity which follows nigrostriatal degeneration may be due to increased effectiveness of synaptic transmission by cholinergic interneurons in the caudate nucleus.

ACKNOWLEDGEMENTS

This work was supported by US Public Health research grants NS 06820 and GM 00162 and by the Medical Research Service of the Veterans Administration.

REFERENCES

BARBEAU, A. (1962) The pathogenesis of Parkinson's disease: A new hypothesis. *Canadian Medical Association Journal*, **87**, 802–807.

BERNARDI, G.; FLORIS, V., MARCIANI, M. D., MOROCUTTI, C. and STANZIONE, P. (1976) The action of acetylcholine and L-glutamic acid on rat caudate neurons. *Brain Research, Amsterdam*, **114**, 134–138.

BLOOM, F. E., COSTA, E. and SALMOIRAGHI, G. C. (1965) Anesthesia and the responsiveness of individual neurons of the caudate nucleus of the cat to acetylcholine, norepinephrine and dopamine administered by microelectrophoresis. *Journal of Pharmacology and Experimental Therapeutics*, **150**, 244–252.

BUTCHER, L. L. and BILEZIKJIAN, L. (1975) Acetylcholinesterase-containing neurons in the neostriatum and substantia nigra revealed after punctate intracerebral injection of di-isopropylfluorophosphate. *European Journal of Pharmacology*, **34**, 115–125.

BUTCHER, S. G. and BUTCHER, L. L. (1974) Origin and modulation of acetylcholine activity in the neostriatum. *Brain Research, Amsterdam*, **71**, 167–171.

CARPENTER, M. B. (1976) Anatomical organization of the corpus striatum and related nuclei. In: *The Basal Ganglia.* Edited by Melvin D. Yahr. New York: Raven Press, pp. 1–36.

CHANG, C. C. (1964) A sensitive method for spectrophotofluorometric assay of catecholamines. *International Journal of Neuropharmacology*, **3**, 643–649.

DUVOISIN, R. C. (1967) Cholinergic-anticholinergic antagonism in Parkinsonism. *Archives of Neurology*, **17**, 124–136.

FIBIGER, H. D. and GREWAAL, D. S. (1974) Neurochemical evidence for denervation supersensitivity: The effect of unilateral substantia nigra lesions on apomorphine-induced increases in neostriatal acetylcholine levels. *Life Sciences*, **15**, 57–63.

HERZ, A. and ZIEGLGÄNSBERGER, S. (1968) The influence of microelectrophoretically applied biogenic amines, cholinomimetics and procaine on synaptic excitation in the corpus striatum. *International Journal of Neuropharmacology*, **7**, 221–230.

HORNYKIEWICZ, O. (1973) Parkinson's disease: From brain homogenate to treatment. *Federation Proceedings*, **32**, 183–190.

JONES, E. G. and LEAVITT, R. Y. (1974) Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. *Journal of Comparative Neurology*, **154**, 349–378.

KATAOKA, K., BAK, I. J., HASSLER, R., KIM, J. S. and WAGNER, A. (1974) L-glutamate decarboxylase and choline acetyltransferase activity in the substantia nigra and the striatum after surgical interruption of the strio-nigral fibres of the baboon. *Experimental Brain Research*, **19**, 217–227.

KEMP, J. M. and POWELL, T. P. S. (1971*a*) The structure of the caudate nucleus of the cat: Light and electron microscopy. *Philosophical Transactions of the Royal Society of London*, **262**, 383–401.

—— —— (1971*b*) The site of termination of afferent fibres in the caudate nucleus. *Philosophical Transactions of the Royal Society of London*, **262**, 413–427.

LYNCH, G. S., LUCAS, P. A. and DEADWYLER, S. A. (1972) The demonstration of acetylcholinesterase containing neurones within the caudate nucleus of the rat. *Brain Research, Amsterdam*, **45**, 617–621.

MCGEER, E. G., FIBIGER, H. C., MCGEER, P. L. and BROOKE, S. (1973) Temporal changes in amine synthesizing enzymes of rat extrapyramidal structures after hemitransections or 6-hydroxydopamine administration. *Brain Research, Amsterdam*, **52**, 289–300.

—— MCGEER, P. L., GREWAAL, D. S. and SINGH, V. K. (1975) Striatal cholinergic interneurons and their relation to dopaminergic nerve endings. *Journal of Pharmacology, Paris*, **6**, 143–152.

MCGEER, P. L., BOULDING, J. E., GIBSON, W. C. and FOULKES, R. G. (1961) Drug-induced extrapyramidal reactions. Treatment with diphenhydramine hydrochloride and dihydroxyphenylalanine. *Journal of the American Medical Association*, **177**, 665–670.

—— MCGEER, E. G., FIBIGER, H. C. and WICKSON, V. (1971) Neostriatal choline acetylase and cholinesterase following selective brain lesions. *Brain Research, Amsterdam*, **35**, 308–314.

MCLENNAN, H. and YORK, D H. (1966) Cholinergic mechanisms in the caudate nucleus. *Journal of Physiology*, **187**, 163–175.

MAICKEL, R. P., COX, R. H., SAILLANT, J. and MILLER, F. P. (1968) A method for the determination of serotonin and norepinephrine in discrete areas of rat brain. *International Journal of Neuropharmacology*, **7**, 275–281.

MARCO, L. A., COPACK, P , EDELSON, A. M. and GILMAN, S. (1973) Intrinsic connections of caudate neurons. I. Locally evoked field potentials and extracellular unitary activity. *Brain Research, Amsterdam*, **53**, 291–305.

MEHLER, W. R. (1966) Further notes on the centrum medianum nucleus of Luys. In: *The Thalamus.* Edited by D. P. Purpura and M. D. Yahr. New York: Columbia University Press, pp. 109–127.

NORCROSS, K. and SPEHLMANN, R. (1978) Decreased sensitivity of caudatal neurons to micro-iontophoretic dopamine in the dopamine-depleted caudate nucleus. *Brain Research, Amsterdam.* In press.

PORTIG, P. J. and VOGT, M. (1969) Release into the cerebral ventricles of substances with possible transmitter function in the caudate nucleus. *Journal of Physiology*, **204**, 687–715.

SIMKE, J. P. and SAELENS, J. K. (1977) Evidence for a cholinergic fiber tract connecting the thalamus with the head of the striatum of the rat. *Brain Research, Amsterdam*, **126**, 487–495.

SPEHLMANN, R. (1975) The effects of acetylcholine and dopamine on the caudate nucleus depleted of biogenic amines. *Brain*, **98**, 219–230.

SPEHLMANN, R. and STAHL, S. M. (1976) Dopamine acetylcholine imbalance in Parkinson's disease. *Lancet*, **1**, 724–726.

STADLER, H., LLOYD, K. G., GADEA-CIRIA, M. and BARTHOLINI, G. (1973) Enhanced striatal acetylcholine release by chlorpromazine and its reversal by apomorphine. *Brain Research, Amsterdam*, **55**, 476–480.

VAN WOERT, M. H., AMBANI, L. and BOWERS, M. B. (1972) Levodopa and cholinergic hypersensitivity in Parkinson's disease. *Neurology, Minneapolis*, **22**, Suppl., 86–93

ZARZECKI, P., BLAKE, D. J. and SOMJEN, G. G. (1976) Interactions of nigrostriate synaptic transmission, iontophoretic o-methylated phenylamines, dopamine, apomorphine and acetylcholine. *Brain Research, Amsterdam*, **115**, 257–272.

(*Received October 11, 1977*)

Brain (1978), **101**, 661-671

MEASUREMENTS OF VISUAL EVOKED POTENTIALS IN PARKINSON'S DISEASE

by IVAN BODIS-WOLLNER *and* MELVIN D. YAHR

(*From the Department of Neurology, Mount Sinai School of Medicine,*
100th Street and 5th Avenue, New York, New York 10029)

INTRODUCTION

IT is a formidable task to establish conduction properties of sensory pathways in the intact human brain. An indirect approach is based on measurements of reaction time. The method requires motor participation and for this reason the interpretation of such measurements in terms of sensory conduction is ambiguous in patients with disorders of movement. It has been proposed that direct measurement is possible with the use of newer techniques of recording evoked potentials. Visual evoked potentials (VEPs) have been utilized as a diagnostic tool to detect slowing of conduction due to central demyelination: the latency of a standard deflection in the evoked waveform is prolonged in patients with optic neuritis and multiple sclerosis (Halliday, McDonald and Mushin, 1973). The reproducibility of the evoked potential waveform from trial to trial, and the remarkably low dispersion of the latency of the VEP of normals, have made visual evoked potential measurements one of the established clinical tests of diagnostic neurology. Results obtained in our laboratory with grating pattern stimuli generally agree with those of other investigators: latency is prolonged in most patients with a previous episode of or acute demyelination of the central nervous system (Bodis-Wollner, Hendley, Mylin and Thornton, 1979). However, in the course of these clinical studies we have encountered another group of patients whose latencies seem to fall outside the normal range, even though their clinical picture and pathology are distinct from multiple sclerosis. These patients have Parkinson's syndrome, a condition generally thought of as involving only motor and not sensory pathways. In this syndrome at least one neurotransmitter (dopamine) has been shown to be deficient and its replacement is capable of relieving the symptoms. In an attempt to develop objective measurements which may aid in the assessment of the disease state and the effect of therapy, we have undertaken a study of VEPs in this disorder. The results in fact suggest the possibility that VEP measurements may be useful in following progression of the disease and the effects of therapy. Furthermore, our findings raise questions concerning the pathophysiology of this disease as it appears to affect conduction in the visual pathways.

METHOD

Patients

Both inpatients and ambulatory volunteer patients with the diagnosis of Parkinson's disease were selected. Only those patients whose visual acuity was better than 6/15 and whose ophthalmological examination disclosed no abnormality of the ocular media or increased intraocular pressure were admitted for study. Also excluded were those whose VEP was so poor that its latency could not be reliably measured. In several patients sluggish pupil reactions were noted; however these patients were included as we found no consistent change of EP latency as a function of pupil reactivity in patients with Adie's syndrome (*see below*) or in normal volunteers with cycloplegia and artificial pupils. The mean age of the 35 patients with Parkinson's disease was 62 years, and the average duration of their disease was 8·1 years. The control population consisted of 26 volunteer patients, 20 of whom were inpatients on the neurology ward. Their mean age was 60 years. Their diagnoses included: transient ischæmic attacks (5), motor neuron disease (4), cerebral concussion (2), Adie's syndrome (2), brain tumour (2), tumour of the cord (1), metastatic disease (1), essential tremor (1), psychoneurosis (4), and 4 patients who were neurologically intact.

Visual Evoked Potentials

(*a*) Stimulus. Vertical gratings with sinusoidal luminance profile were generated on the screen of a Tektronix 561 oscilloscope. The CRT screen subtended 3·8 degrees at the observer's eye. It was surrounded by another screen subtending 16 degrees. This screen was back-illuminated at about the same hue and luminance as the CRT to ensure constant light adaptation of the observer's foveal region. The space-time average luminance of the screen was held constant at 4 cd/m^2. The spatial frequency of the grating was 2·3 cycles/degree. Spatial frequency of a grating pattern is expressed as the number of alternating pairs of dark and bright bands subtending 1 degree of visual angle at the observer's eye. The contrast of the grating was 0·7. Spatial contrast is the ratio of the difference of maximum and minimum luminance of adjacent bands over their summed luminance

$$C = L_{max} - L_{min} / L_{max} + L_{min}$$

The grating was modulated at the rate of 1 Hz in a 'suppressed carrier mode' producing a pattern reversal of 2 per second. The modulating signal was obtained by dividing the horizontal sweep signal of the oscilloscope and it triggered the signal averager (*see below*).

(*b*) *EP recording*. Silver disc surface electrodes were pasted in a mid-occiput (2·5 cm above the inion)—right posterior temporal—montage (Bodis-Wollner, Hendley and Kulikowski, 1972). The forehead electrode was grounded. For several patients we compared EPs referred simultaneously to the midfrontal and to the posterior temporal electrode. While the latter record tended to have smaller amplitude and the former was more often distorted by eye movement artifacts, latencies were not significantly different. Potentials referred to the 'active' occipital electrode were differentially amplified with a Grass Model 5 EEG apparatus. Filters were set at 0·2 and 50 Hz with half bandwidth extending one octave. Signals were averaged on a Nicolet 1072 signal averager.

(*c*) *Measurements*. Following the method of Halliday *et al*., (1973), the latency of the evoked potential was measured as the time from the onset of the pattern reversal to the peak of the major positive EP deflection recorded at the occipital electrode (fig. 1).

(*d*) *Comparing VEP latency of patients and normals*. The covariance matrix and the mean of all right eye latencies and all the left eye latencies were compared between controls and patients with Parkinson's disease. A multivariate analysis (Timm, 1975) was used to test the null hypothesis that the mean response of the control group is equal to that of the group with Parkinson's disease. Discriminant analysis (Rao, 1973) was used to calculate the number of patients with Parkinson's disease who would have been classified as normal controls, and *vice versa* Linear regression was used to test correlation between variables of age, duration of disease, and latency of the VEP as explained in the Results.

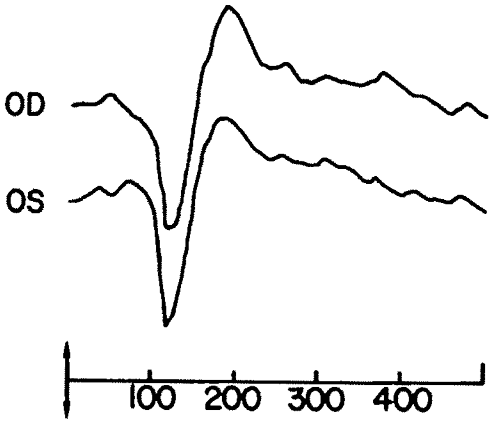


FIG. 1. Normal latency (126 ms) of the major positive wave (downward deflection) in both eyes of a 55 year-old patient who was treated for Parkinson's disease for ten years. The double arrow at line zero shows the onset of the stimulus reversal, and its amplitude represents 5 μv in this and subsequent figures. In this and subsequent figs. OD = stimulation of R. eye and OS = stimulation of L eye.

RESULTS

A. *The Latency of the VEP in the Control Group*

In the control group the mean EP latency was 116±9 ms (SD). OD and OS and the average interocular difference was 3±3·5 ms (SD). The 95 per cent confidence limit of the normal interocular difference was 10 ms, while the upper 95 per cent limit of the normal latency was 134 ms.

B. *VEP Latency in Patients with Parkinson's Disease*

In 35 patients the mean evoked potential latency was 139±22 ms OD and 143±28 ms OS, and the average interocular difference was 13±17 ms (SD). In 19 patients this difference was above 14 ms. Two patients had an interocular latency difference of more than 70 ms. In 2 patients who were initially not treated, the latency returned toward normal in one eye only so that an interocular latency difference appeared on treatment.

C. *Comparison of the EP Latency of the Control Group and of Patients with Parkinson's Disease*

When comparing the two groups, all tests were performed with and without including the data of the 2 Parkinsonian patients who had EP latencies in one or both eyes above 200 ms (*see* fig. 2). The statistically significant difference between the Parkinsonian and Control Group remained the same. The multivariate test rejected ($P<0·01$) the hypothesis that 'Control' and Parkinsonian patients are indistinguishable by EP latency and belong to the same population. The Control Group data were then used to estimate the mean response and covariance matrix for a bivariate normal distribution. An ellipse, representing 95 per cent probability of belonging to the Control Group was determined, as shown in fig. 2. Using a discriminant function (Rao, 1973) which was developed from the data of the Control and Parkinsonian patients, 12 of the latter would have been classified as 'Control', or conversely, 24 of the 36 Parkinsonian patients had EP latencies outside the Control Group of neurological patients.

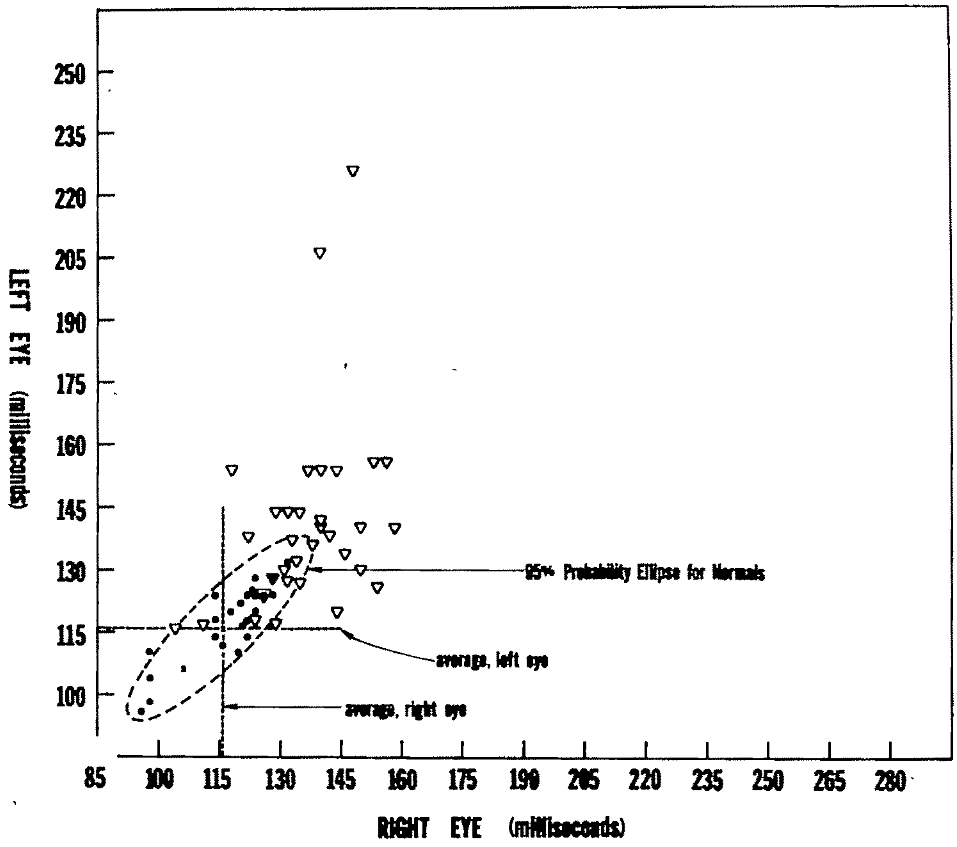


FIG. 2. Scattergram showing the latency of the major positive EP deflection in 35 patients with Parkinson's disease (▽) and 26 control patients (●). Numerals indicate the number of measurements falling on the same locus. Values for the left and right eye are shown on the ordinate and abscissa, respectively. An ellipse has been drawn within which 95 per cent of the normal population would be expected to fall, based on the statistics of the control group Over two-thirds of patients with Parkinson's disease are outside this ellipse

D. *The Effect of Age*

A small but significant trend toward increasing EP latency with age (1·7 ms/decade) has been reported for normal observers (Celesia and Daly, 1977). In our Parkinsonian Group the correlation between age and VEP latency was not significant. In order to demonstrate this lack of correlation we calculated the latency for Parkinsonian patients in four age groups: 40 to 58, 58 to 63, 64 to 69, and 70 to 75 years. The respective mean values were 134, 137, 146 and 135 ms.

E. *The Effect of Duration of Disease*

We tried to estimate the duration of each patient's disease from their first symptoms until the testing date. There was inverse correlation between the duration of treated Parkinson's disease and the latency of the EP for patients who were classified as abnormal according to the discriminant analysis. This correlation reached statistical significance of $P<0{\cdot}01$ only for the right eye, while the correlation was above $P>0{\cdot}01$ for the other eye.

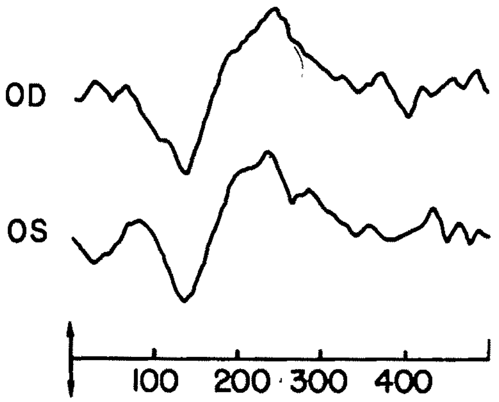


FIG. 3. Increased VEP latency in the right eye (OD· 140 ms) and the left eye (OS: 142 ms) of a 75 year-old patient with visual acuity of 6/6 in either eye. This patient had neither anticholinergic nor dopaminergic treatment for Parkinson's disease prior to this recording.

F. *The Effect of Treatment*

Among patients whose EP latency was classified as abnormal, there were those who did receive and those who never received anticholinergic medication (fig. 3). However in a subgroup of 10 patients who never received dopaminergic therapy, the mean latency was higher (143 ms OD and 151 ms OS) than in the total group of Parkinsonian patients. The mean age of the untreated group was 61 years (compared to 62 for the total group). The mean duration of their disease was five years. Three of the 10 patients could be classified as normal, according to the discriminant analysis. Two of these had had symptoms for three years while the third patient was newly diagnosed. In 2 patients the initially delayed EP returned to normal in both eyes on L-dopa therapy (*see* fig. 4). In another patient the latency became less delayed in both eyes, symmetrically decreasing to 140 ms, while in 2 patients the latency became less in one eye only on therapy. In one patient the latency was already prolonged (140 ms OD and 150 ms OS) on Sinemet (levodopa and carbidopa) therapy. When this therapy was discontinued for ten days the latency became even further delayed in the left eye (202 ms). In the right eye, the response became atypical and the latency measurement was somewhat equivocal. Keeping the definition of the 'major positive wave', however, would suggest in the right eye, similar to the left eye, a shift of the EP latency to 204 ms after discontinuation of therapy.

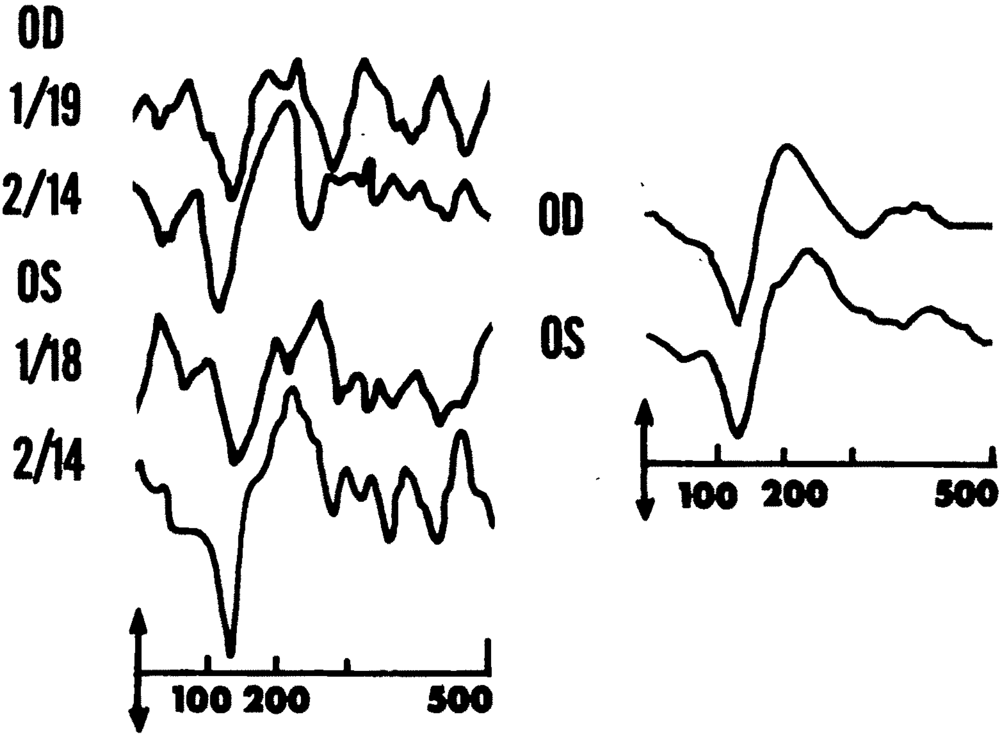


FIG. 4. *Left*: increased latency in both eyes of a 64 year-old patient prior to treatment (1/19, OD: 138 ms; OS: 144 ms) Following treatment with Sinemet (levodopa with carbidopa) the latency became shorter (2/14, OD: 120 ms; OS: 128 ms). *Right*. marginally increased EP latency is shown for a 71 year-old patient despite three years of treatment with Sinemet (OD: 133 ms; OS: 137 ms).

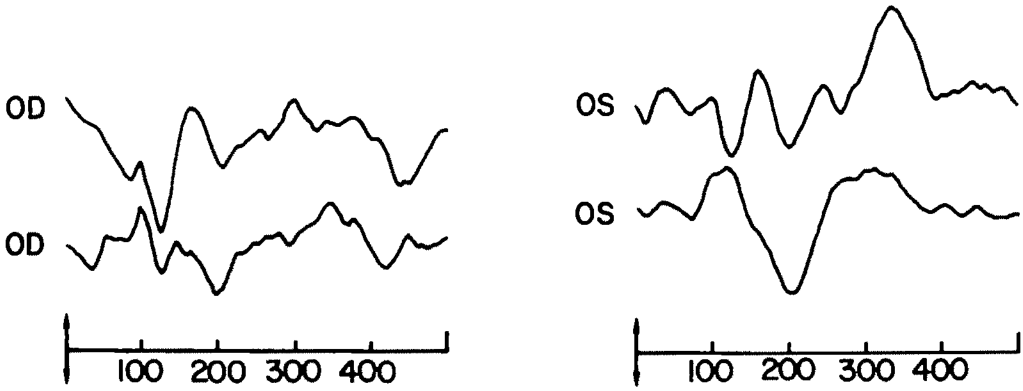


FIG. 5. *Top, left and right*. increased latency in the right eye (OD: 140 ms) and the left eye (OS· 150 ms) of a 71 year-old patient with a three year history of Parkinson's disease. He was treated with Sinemet. *Bottom*: on discontinuation of therapy for ten days, in the right eye (*bottom left*) the latency measurement of the 'major' positive deflection is 204 ms, but there is an early, small, positive deflection with a latency equal to the EP latency before discontinuation of Sinemet therapy (*top left*). In the left eye however, there is a clear-cut increase of the EP latency (*bottom right*) where it now measures 202 ms

Illustrative Case History of a Patient with Unexplained Difference in Interocular EP Latency

This 69-year-old lady first noted tremor of the right hand in 1969. Shortly thereafter she developed tightness in her hand, and became aware of slowness in movement, especially walking. In 1970, when she was 70 years old, the diagnosis of Parkinson's disease was made, and her treatment began with anticholinergic medication. Her condition continued to progress and in 1973 amantadine was added to her regimen. There was further progression and she was started on Sinemet (levodopa and carbidopa) 10/100 mg t.i.d., while her other medications were discontinued. She noted that when reading the newspaper the lines became fuzzy and that her vision became blurred several times a day, most noticeably in the morning. She had no trouble finding objects, and she denied double vision. Her pupils reacted somewhat slowly, slightly better to light than to convergence and accommodation. Ophthalmological examination in 1975 disclosed visual acuity of 6/6 in each eye; the cornea, the lens and posterior pole were clear, and her interocular pressure was 12 in each eye as measured by the Goldman applanation tonometer. At the end of 1975 she noted a 'heavy lid' which would on occasion make it difficult for her to keep the left eye open. Examination revealed intact eye movements and good convergence. Visual acuity was 6/7·5 OU, fundi were negative, and reaction of the pupil remained somewhat sluggish. Her Parkinson's disease was well controlled in the ensuing years on Sinemet alone, although morning stiffness of the left leg was noted. Her repeat ophthalmological examination in 1978 disclosed no change. Her visual evoked potential testing was performed in 1977 and 1978, and both times showed abnormal interocular difference. The pupil size was around 3–4 mm in each eye at the EP testing and visual acuity was 6/7·5 OU. Latency in the *right* eye remained 144 ms (fig. 6), while in the *left* eye it was 120 ms.

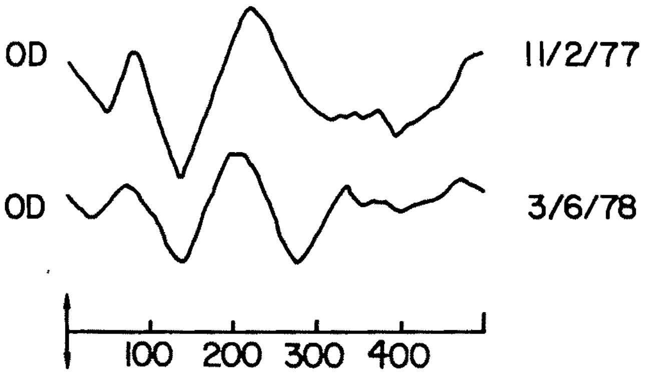


FIG. 6. Identically increased latency (144 ms) recorded at interval of four months in the right eye of a 77 year-old patient whose history is described in the text Latency was normal (120 ms) in the left eye on both occasions.

DISCUSSION

Visual evoked potentials elicited by patterned stimuli are predominantly determined in the primary pathways of the human visual system. There is a large body of evidence that grating patterns are optimal stimuli for neurons in the primary visual cortex, and there is an impressive correlation between pattern EPs and visual functions. This correlation is not always simple. While *amplitude* changes of pattern evoked potentials correlate with changes of visual acuity and contrast sensitivity in lesions of the primary pathways (Bodis-Wollner, 1976), an abnormal *latency* of the pattern EP which is found in the majority of patients with multiple sclerosis does not correlate with either visual acuity or spatial contrast sensitivity to grating patterns (Bodis-Wollner, Hendley, Mylin and Thornton, 1979). It is thought that abnormal latency is due to delayed conduction in visual pathways affected by the process of demyelination and/or plaque formation. Long delays may be caused by conduction in denuded axons in the retino-geniculo-calcarine pathway (McDonald, 1977).

It is surprising to find delayed VEPs in patients with Parkinson's disease, as neither involvement of visual pathways nor demyelination is a characteristic feature. Hence one must consider alternate mechanisms and/or pathways as playing a role. Perhaps in Parkinson's disease there is an altered, indirect influence of the basal ganglia on the generation of visual evoked potentials. Anatomical considerations point to striatotectal connections. It has been shown that stimulation of the caudate nucleus inhibits EPs in the visual cortex of the cat (Demetrescu and Demetrescu, 1962), and in this animal there are nigrotectal connections (Graybiel, 1978), as has been shown also in the monkey (Carpenter and McMasters, 1964). Pathways from the substantia nigra to the superior colliculus form synapses just below the layer where ipsilateral retinal efferents establish their contacts with collicular neurons possessing 'visual-motor' receptive fields. Pathways from the superior colliculus to the visual cortex have been demonstrated (Palmer, Rosenquist and Sprague, 1972). Since the latency of the major positive deflection of the normal VEP to grating stimuli is about 100 to 120 ms, there is sufficient time for nigrotectal polysynaptic pathways to affect this 'component' of the visual evoked potential.

Since in some patients we found that the EP latency became shorter under dopaminergic therapy, it is possible that either striatal or extrastriatal catecholaminergic pathways affect the visual evoked potential. It is known that Parkinson's disease affects several areas of the nervous system and one may suspect that other catecholamines besides dopamine are involved (Riederer, Birkmayer, Seemann and Wuketich, 1977). In this regard it may be relevant that noradrenergic pathways from the locus caeruleus to the visual cortex determine the development of binocular neurons of the cat (Kasamatsu and Pettigrew, 1976). The effects of another neuropharmacologically active substance point, however, to the possible role of dopamine itself in VEP changes in Parkinson's disease. Chlorpromazine administration changes the evoked response in the superior colliculus to *diffuse flashes*, but does not affect the response in the visual cortex (Bakay and Mirsky, 1977). Given the known dopaminergic antagonist effect of chlorpromazine, it would be of interest to study the effect of dopamine and the role of the superior colliculus in the evoked response of the primate visual cortex to *patterned stimuli*.

An important site of further study may be the retina itself. Although all our patients were normal on ophthalmological examination, we cannot exclude involvement of the direct visual pathway in Parkinson's disease as a cause of delayed VEP. In 19 of the 35 patients, a significant interocular latency difference was present in the visual evoked potential. Interocular differences could imply prechiasmal, possibly retinal delays. Dopamine is widely found in the retina of many species, including monkeys, cats, rabbits and rats. It is now well established that dopamine is a neurotransmitter for interplexiform cells of new world monkeys (Dowling, Ehinger and Hedden, 1976). Certainly the notion of retinal dopaminergic impairment as a cause of prolonged EP latency is consistent with the concept of Parkinson's disease as a generalized dopaminergic deficiency syndrome (Barbeau, Campanella, Butterworth and Yamada, 1975). At present, however, there is only scant evidence for dopamine in the human visual pathways.

Whatever explanation of increased VEP latency in Parkinson's disease may emerge, the monitoring of visual evoked potentials may be useful in the objective assessment of the disorder as well as of its response to treatment. Patients with Parkinson's disease were often included in the 'control' population in previous VEP studies, using checkerboard stimuli. With this stimulus only minor EP latency changes can be found in patients with Parkinson's disease (Davison, R. H., 1978; Dell, S., 1978, personal communication), thus their inclusion as controls may have been inconspicuous. In most laboratories the size of the individual checks of the stimulus, and even more commonly the total stimulus area, is larger than our gratings, and in addition, the luminance of our stimulus is lower. It is not yet certain which of these differences is crucial, but it appears important to specify, in further clinical studies of VEP latency, the precise stimulus conditions.

Two-thirds of all patients with Parkinson's disease had abnormal EP latency: there were both treated and untreated patients who had normal EP latency regardless of the duration of their disease. The correlation between prolonged VEP latency and duration of the disease was significant for patients with abnormal latency when interocular differences were neglected. It is noteworthy that patients with Parkinson's disease have been subdivided into a 'malignant' and 'benign' group, based on slow *versus* fast clinical evolution (Hoehn and Yahr, 1967; Marsden and Parkes, 1977). It remains to be seen in long-term follow-up whether or not changes in EP latency and clinical progression will correlate with each other.

SUMMARY

Visual evoked potentials elicited by reversing grating patterns were recorded in 35 patients with Parkinson's disease and in 26 controls. The average latency of evoked potentials in patients with Parkinson's disease exceeded by two standard deviations the average of the age-matched control group of other neurological patients. Over two-thirds of all patients with Parkinson's disease had abnormal latency. In these patients latency did not correlate with age. In 5 patients the latency became less prolonged on levodopa therapy, suggesting that catecholaminergic pathways have either indirect or direct effects on the generation of visual evoked potentials. Extrapyramidal connections of the visual cortex, as well as retinal dopaminergic neurons, require further study in Parkinson's disease.

ACKNOWLEDGEMENTS

We thank Drs. Allen Moss and Murray Wolkstein for ophthalmological evaluation of the patients, and Dr. John Thornton for helping with the statistical evaluation of the data. Mr. Leland Mylin has given invaluable technical assistance.

This work was supported in part by The Clinical Center for Parkinson's Disease and Allied Disorders, Grant No. NS 11631-5, the National Eye-Institute, Grant No. EY 01708, and National Institutes of Health Grant No. RR-00071, Division of Research Resources, General Clinical Research Center Branch.

REFERENCES

BAKAY, E. P. and MIRSKY, A. F. (1977) Effect of secobarbital and chlorpromazine on cortical and subcortical visual-evoked potentials in the monkey. *Psychopharmacology Bulletin*, **13**, 61–64.

BARBEAU, A., CAMPANELLA, G., BUTTERWORTH, R. F. and YAMADA, K. (1975) Uptake and efflux of ^{14}C-dopamine in platelets: evidence for a generalized defect in Parkinson's disease. *Neurology, Minneapolis*, **25**, 1–9.

BODIS-WOLLNER, I. (1976) Vulnerability of spatial frequency channels in cerebral lesions. *Nature, London*, **261**, 309–311.

—— HENDLEY, C. D. and KULIKOWSKI, J. J. (1972) Electrophysiological and psychophysical responses to modulation of contrast of a grating pattern. *Perception*, **1**, 341–349.

—— —— MYLIN, L. H. and THORNTON, J. (1979) Visual evoked potentials and the visuogram in multiple sclerosis. *Annals of Neurology*, **5**.

CARPENTER, M. B. and MCMASTERS, R. E. (1964) Lesions of the substantia nigra in the rhesus monkey. Efferent fiber degeneration and behavioural observations. *American Journal of Anatomy*, **114**, 293–320.

CELESIA, G. G. and DALY, R. F. (1977) Effects of aging on visual evoked responses. *Archives of Neurology, Chicago*, **34**, 403–407.

DEMETRESCU, M. and DEMETRESCU, M. (1962) The inhibitory action of the caudate nucleus in cortical primary receiving areas in the cat. *Electroencephalography and Clinical Neurophysiology*, **14**, 37-52.

DOWLING, J. E., EHINGER, B. and HEDDEN, W. L. (1976) The interplexiform cell: a new type of retinal neuron. *Investigative Ophthalmology*, **15**, 916-926.

GRAYBIEL, A. (1978) Organization of the nigrotectal connection: an experimental tracer study in the cat. *Brain Research, Amsterdam*, **143**, 339-348.

HALLIDAY, A. M., MCDONALD, W. I. and MUSHIN, J. (1973) Visual evoked response in the diagnosis of multiple sclerosis. *British Medical Journal*, **4**, 661-664.

HOEHN, M. M. and YAHR, M. D. (1967) Parkinsonism: onset, progression, and mortality. *Neurology, Minneapolis*, **17**, 427-442.

KASAMATSU, T. and PETTIGREW, J. D. (1976) Depletion of brain catecholamines: failure of ocular dominance shift after monocular occlusion in kittens. *Science*, **194**, 206-209.

MARSDEN, C. D. and PARKES, J. D. (1977) Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet*, **i**, 345-350.

MCDONALD, W. I. (1977) Pathophysiology of conduction in central nerve fibres. In: *Visual Evoked Potentials in Man.* Edited by J. E. Desmedt. Oxford: Clarendon Press, pp. 427-437.

PALMER, L. A., ROSENQUIST, A. C. and SPRAGUE, J. M. (1972) Corticotectal systems in the cat: their structure and function. In: *Corticothalamic Projections and Sensorimotor Activities.* Edited by T. Frigyesi, E. Rinvik and M. D. Yahr. New York: Raven Press, pp. 491-523.

RAO, C. R. (1973) *Linear Statistical Inference and Its Applications*, New York: John Wiley, pp. 574-577.

RIEDERER, P., BIRKMAYER, W., SEEMANN, D. and WUKETICH, S. (1977) Brain noradrenaline and 3-methoxy-4-hydroxyphenyl-glycol in Parkinson's syndrome. *Journal of Neurological Transmissions*, **41**, 241-252.

TIMM, N. H. (1975) *Multivariate Analyses.* Belmont, California: Wadsworth Publishing, p. 261.

(*Received May 30, 1978*)

Brain (1978), **101**, 673-685

THE CONCEPT OF A SENSORIMOTOR CORTEX

ITS EARLY HISTORY, WITH ESPECIAL EMPHASIS ON TWO EARLY EXPERIMENTAL CONTRIBUTIONS BY W. BECHTEREW[1]

by ALFRED MEYER[2]

(*Formerly at the Institute of Psychiatry, The Maudsley Hospital, London*)

INTRODUCTION

THE concept of a sensorimotor cortex is generally attributed to Munk. Although he is usually quoted from the second edition of his *The Functions of the Cerebral Cortex* published in 1890, Munk's views of this particular part of the cortex are essentially the same as those which he had expressed in the first edition of 1881, of which the relevant third chapter ('Mitteilung') has been reproduced by von Bonin (1960). Munk considered the cortical motor field to be part of the 'feeling sphere' in the large region in front of the visual and auditory centres in the dog's brain (C, D, E in Munk's figures). He spoke of a 'cortical' or 'psychical' paralysis (his 'Rinden-' or 'Seelenlähmung') caused by the loss of the memory for sensory images of motor action. Nowhere have I found any mention of a 'sensory-motor cortex'. Early allusions to this term were made by Luciani (1884, whose paper will be discussed on p. 675), by Hughlings Jackson (1884, p. 61) and again in the discussion to the paper by Bastian (1887) where, on p. 107 Jackson spoke of 'sensorimotor units', effective on cortical, subcortical and spinal levels, and by Mott (1894) who headed a paper 'The sensory motor functions of the central convolutions'.

Mott's paper is of considerable historical interest, as it reveals the confusion which surrounded the concept of the 'sensorimotor cortex'. He distinguished three groups of workers on the subject: the first of those who regarded the Rolandic region as purely *motor*, the second who held it to be purely *sensory*, and a third who regarded it as mixed sensory motor. Mott himself associated himself firmly with the third group.

---

[1] A more accurate spelling would be 'Vladimir Bekhterev', as used by Paul Jakovlev in *The Founders of Neurology* (Haymaker and Schiller, 1970) However, in the German translations from which I quote, he spelled his name 'W. Bechterew', in later years adding the ennobling 'von'

[2] Requests for reprints should be addressed to 38, Wood Lane, Highgate, London, N6 5UB.

The first group was led by Ferrier (1876, 1886, 1887, 1890). In the first edition of his *The Functions of the Brain* of 1876 (of which I quote from excerpts on pp. 199–202 (Clarke and O'Malley, 1968)) Ferrier said of his experiments on monkeys in which he was the first to use stimulation by faradic currents: 'The first experiment I have to record is instructive, as showing the respective effects of irritation and destruction of the convolutions bounding the fissure of Rolando. . . . The part exposed included the (right) ascending parietal, ascending frontal and posterior extremities of the frontal convolutions. . . . Tactile sensation, as well as sight, hearing, smell and taste, were retained. On *post-mortem* examination it was found that the exposed convolutions were completely softened, but beyond this the rest of the hemisphere and the basal ganglia were free from injury . . .'.

In 1886 and later in 1887 in the discussion to Bastian's paper on p. 95, Ferrier strongly reaffirmed his views: 'the motor centres are motor centres in precisely the same sense as other motor centres. Excitation causes movement, destruction causes paralysis of movement, and of this only'. Again he stressed that after lesion of the Rolandic convolutions there was no 'loss or impairment of tactile or muscular sensibility'. Horsley and Schäfer (1888) fully supported Ferrier's findings. Even in 1891, Beevor and Horsley reported no sensory impairment although their diagrams in stimulation experiments on monkeys and apes clearly indicate that the boundary lines pass across the fissure of Rolando, particularly in the important lower two-thirds of the postcentral region. However, Mott reported that later in 1891 Horsley began to waver towards a mixed sensorimotor function of the Rolandic region. By 1894 Horsley had five human cases in which large portions of the brain in the Rolandic region had been removed and the operation had been followed by sensory as well as motor defects: Mott was able to confirm this personally in two of these. Horsley insisted on mixed sensorimotor function in both Rolandic regions as late as 1909 in his Linacre lecture—seven years after Grünbaum and Sherrington's first report that the postrolandic zone was inexcitable (1902), and two years after the Vogts (1907), also in monkeys, had confirmed Sherrington's findings. Horsley's error was part of his generally recognized emphasis on the close integration of many centres in the control of movement. In this he adopted Jacksonian ideas.

Schäfer, the partner of Horsley in 1888, was slower in the retreat from his original position: even in 1898—although he admitted that 'Hemianæsthesia sometimes results from an extensive lesion of the motor cortex' (that is, both convolutions bordering the sulcus of Rolando)—he pointed out that 'this is however not local but general, and is due to the vascular and mechanical disturbance produced upon the whole side of the brain by the establishment of the lesion'. But now he conceded that hemianæsthesia may not be caused by a hippocampal lesion (as suggested by Ferrier and Yeo, 1884) nor by a defect in the gyrus fornicatus as advocated by Horsley and himself (1888), but rather be 'due to the general disturbance in the whole half of the brain . . .'. Schäfer reaffirmed this view in 1900.

Carville and Duret (1875) and Luciani and Tamburini (1878) have been acclaimed as supporters of Ferrier's views. However, the French authors believed (p. 483) that cortical lesions produced only inconstant and incomplete pareses. They became complete ('véritable') only when the basal ganglia were involved. Luciani and Tamburini spoke of 'psychomotor' pareses after lesions of the Rolandic zone.

Schiff (1875) was regarded by Mott as the chief representative of his second group: for him the central convolutions were purely sensory (but according to Schäfer, Schiff amended his view later). Nothnagel (1873), Hitzig (1874, 1877) and Bastian (1887) were among others who according to Mott regarded the excitable area as the seat of 'muscle sense' or 'kinæsthesis'. Munk was regarded by Mott to belong to his third 'mixed' group, but he might be better placed in the second group, since, as already mentioned, he regarded paralysis to be caused by the loss of the memory for sensory images.

The concepts of 'muscle sense' or 'sense of innervation' are derived from Charles Bell and from some of the disciples of Johannes Müller and their followers, in particular Wilhelm Wundt, whose views were introduced into this country by Bain (1864). The history of these concepts has recently been fully reviewed by Jones (1972, *see there also* for references).

Into his third mixed sensorimotor group Mott included Hughlings Jackson (1887 in the discussion to Bastian's paper and again in 1890) for whom on theoretical grounds a separation of sensory from motor centres was unthinkable. From 1881 Jackson spoke of the sensorimotor region in the Rolandic convolutions as the *middle level*, the highest level being located in the prefrontal cortex. On the other hand, he considered the visual cortex in the occipital lobe to be the highest cortical level of vision. Not until 1898 did he admit this injustice, by relegating the visual cortex to the status of 'middle level', subsidiary to a highest level of vision, though he confessed his ignorance of its location.

Others in Mott's third group were Luciani and Seppili (1885), Starr (1884), Dana (1888) and Bechterew (1899). Luciani and Seppili's monograph was not available to me but in 1884 Luciani (p. 157) gave a preview of their conclusions:

> . . . consequently to the total or partial extirpation of the motor zone in the dog and the monkey, one constantly observes effects not only of motor paralysis, but also of cutaneous and muscular anæsthesia . . . the single centres in the sensory-motor zone are so completely bound up with, and so to speak, let into, one another, that it is not possible to divide them with a clear and definite line . . .

Luciani and Seppili also investigated 47 human cases. These were included in Dana's collection of 142 human cases, who came to conclusions similar to those of the Italian authors.

Starr (1884) reported his experiences in 30 human cases on which he had carried out a cerebral operation. He concluded (pp. 403 and 404) that the various sensory areas for different parts of the body lie about and to some extent coincide with the motor areas for similar parts; sensory perceptions occur in the gray matter of the anterior and posterior central convolutions and of the parietal convolutions.

Mott quoted Bechterew from the first edition of his *Leitungsbehnen* (Tracts of Conduction) of 1894 which was not available to me; but in the second edition of 1899 (p. 432), Bechterew's views were still essentially the same:

> The cortical motor field therefore consists of several sensitive-motor centres, in which under control of tactile and muscle sensations movements are brought about. Stimulation of these centres results in muscle contraction and abnormal sensation in the corresponding (predominantly contralateral) limbs. Ablation results in paralyses of both motor and sensory nature.

Even in 1911 (p. 1476, ff.), after he had taken note of the results of Grünbaum and Sherrington, Bechterew still believed that fibres may cross over in the depth of the Rolandic sulcus.

Forgotten Early Papers by W. Bechterew

Mott knew of Bechterew's paper of 1883 in which Bechterew had reported his findings following ablation of the sigmoid cortex in dogs, but did not comment on it. However, it deserves a more extensive quotation (pp. 411, ff.):

> . . . Upon these data I could conclude with conviction, that after destruction of the motor region the observed motor disturbances do not depend on any sensory changes, and that for this reason the centres of tactile and muscle sense must be separate from the motor centres. After further investigations undertaken in order to determine as accurately as possible the localization of the cortical centres for skin and muscle sensation, I paid attention to the area lying between the motor field which is almost exclusively situated within the sigmoid nucleus and its immediate neighbourhood, and the centres for vision and hearing in the occipital and temporal regions made known to us by the investigations of Ferrier and Munk, respectively.
>
> The function of this large area which would correspond to the parietal convolutions of the human brain, has not yet been investigated by physiologists. Although in his illustration of cortical sensory centres Munk assigned this area to the sensibility of eyes and head, one nevertheless sees at first glance that it would seem strange if such a considerable part of the sensory cortical surface should be reserved for a relatively small part of the body.
>
> By my experiments in dogs which I carried out during several months, I have become convinced that destruction of different points within this area is unfailingly followed by significant sensory changes on the contralateral side of the body. According to the site of the lesion, these changes involve either tactile sensibility or muscle sense or pain.
>
> If the ablation is placed immediately behind the sigmoid gyrus the following signs are usually found, after the animal had recovered from the operation:
>
> 'When I applied strong painful stimuli, for example pin-prick, pressure upon the paws, burning heat or faradisation, I found no difference in reaction between the left and right side body halves. However, if I employed weak stimuli, light touch with the blunt end of the pin, light pressure on different contralateral parts of the body, I noticed that the animal did not react at all, as if it did not perceive them; whereas the same stimuli applied to the ipsilateral side produced movements which must be considered to be normal responses to the stimuli. Incidentally facial tactile sensation was usually unaffected except when the ablation included that part of the second primitive gyrus ("Urwindung") which lies immediately outside the sigmoid convolution. Motor disturbances were absent.
>
> 'If the cortical area between the posterior border of the sigmoid gyrus and the temporal pole had been ablated in the region of the third and fourth primitive gyri—that is to say at the beginning of the fossa Sylvii—I usually observed no changes of tactile sensitivity; instead constant and most distinct defects of the muscle sense appeared in the contralateral extremities. Following passive extension or flexion, or change of position, the blindfolded animal made no correcting movement which might indicate that it had perceived these positional changes . . .'

Bechterew observed also reduction of the normal response to painful stimuli in the contralateral extremities after ablation in the region of the cortical zone responsible for kinæsthetic disturbances. I omit full quotation of this part of his paper because the cortical representation of pain has proved complex and is even today not yet fully understood. Bechterew concluded his paper with the following summary:

'All the experiments reported above provide proof that, within the cortex, separate centres exist for the perception of tactile sensation, muscle sense and of pain. The centres for tactile sensation lie immediately behind and outward of the motor field, whereas the centres for muscle sense and pain are found at the beginning of the fossa Sylvii.

'As evident from the description, the last two centres are close to each other; but because in some animals reduction of muscle sense alone was found, while in others reduced reaction to painful stimuli only, it must be concluded that they are not identical.'

In 1885, Bechterew returned to the subject. The larger part of the new paper argues against the views of Schiff (who, it will be remembered, was the chief representative of Mott's second group). This second paper, however, is noteworthy because, in order to amplify his previous findings, Bechterew reported the results of an ingenious experiment carried out in a cat. He chose this species of carnivores because 'As is well known, cats possess an especially fine sensitivity and are therefore particularly suitable for investigations of tactile sensations' (1885, pp. 143, ff.).

'Using anæsthesia, I trephined the skull wide enough to have access to the left sigmoid gyrus. Then I stimulated the surface with a weak current and determined the localization of the motor centres for the fore- and hindlimbs, marked their extent cautiously with the point of a knife and, with the help of a teaspoon, I ablated the grey matter within the markings until the white matter became visible. The extirpation of the grey matter did not reach the posterior border by 2–4 mm and therefore its effect was unlikely to exceed the limits of the sigmoid gyrus.'

After the operation Bechterew observed motor disturbances which were particularly distinct during the first phase after recovery. These he described convincingly. He continued:

'Investigation of tactile sensation showed that on light touch or caressing of the skin of ear lobes, head and extremities on both sides, the animal almost always reacted with closing the eyes, moving the ear lobes . . . The cat was also highly sensitive to wetting the skin of the paws with a weak jet of water from a syringe . . .

'The manifestations described above were present immediately after recovery from the operation as well as later. In contrast the motor disturbances and the gait improved early—to a degree that it was possible to detect a certain clumsiness of the right extremities on close observation only.

'To me the result of this experiment is completely convincing and needs no further explanation. Obviously, in the absence of even the slightest defect in the sensory response to the usual stimuli, it appears quite impossible to maintain the view that motor disturbances are the consequence of prior involvement of sensory centres.'

In both papers Bechterew emphasized that he had used only weak stimuli for both the exploration by the faradic current of the motor field and for the examination of sensation, in contrast to Ferrier's much stronger stimulations.

DISCUSSION OF BECHTEREW'S FINDINGS

The observations and conclusions of Bechterew must be seen against the background of the confusions and errors which surrounded the problem of the cortical representation of motor and somatosensory function at that early period. Ferrier believed throughout that both Rolandic convolutions controlled motor function; in carnivores they were situated in front of and behind the cruciate sulcus which he regarded as the homologue of the primate's central sulcus. Control of somatosensory function he placed into the hippocampal region. Horsley and Schäfer (1888) shared the views of Ferrier except that they localized somatosensory function into another part of the limbic lobe, the gyrus fornicatus. Although Hitzig (1874) had shown that lesions placed in the sigmoid gyrus resulted in motor disturbances, he, like Schiff, believed that the function of the 'excitable cortex' was 'kinæsthetic' and the motor phenomena were secondary to stimulation of subcortical centres.

Bechterew was the first to demonstrate experimentally that lesions 'almost exclusively confined to the sigmoid nucleus resulted in *purely* motor disturbances.' The cortical somatosensory centre he found lying between the posterior border of the sigmoid nucleus and the auditory and visual cortical centres, in an area of which he said that it had not yet been investigated before by physiologists. He even noticed an anteroposterior representation of tactile sensation and of 'muscle sense'.

These are remarkable results, because they anticipate in carnivores some of the fundamental results of Grünbaum and Sherrington (1902, 1903) in apes by almost two decades and the charting of the somatosensory cortex by an even longer period.

In their final paper of 1917, Leyton (the name adopted by Grünbaum since 1915) and Sherrington stated that in subhuman primates they never succeeded in obtaining motor responses to stimulation of the free surface of the postcentral region except for 'echo' motor responses when faradization of the postcentral gyrus near the central sulcus followed immediately on stimulation of the corresponding part in the motor cortex. Even in that part of the motor cortex buried within the central sulcus the excitable zone was almost entirely confined to the anterior wall: only exceptionally 'in some individuals' did the authors obtain motor responses to stimulation of the deepest and most ventral parts of the posterior wall.

Sherrington and his associate did not extend their experiments to the somatosensory cortex. Cushing (1909) was the first to produce sensation without movement in man by stimulating the postcentral gyrus of two conscious patients; both reported sensations of tingling and numbness in bodily parts which closely corresponded with analogous motor phenomena in the precentral convolution. A confirmation of the anteroposterior representation of tactile and deep sensation had to wait much longer. During their stimulation experiments in the human cortex, Penfield and Rasmussen (1950) found that 'discriminatory' sensation was represented in areas 1 and 3, and 'proprioceptive' sensation more caudally in area 2. Their results were confirmed in monkeys by Powell and Mountcastle (1959) and by Jones and Powell (1969). Retrospective judgement, however, would look for a loss of joint sensibility rather than of 'muscle sense' to explain the 'positional' changes reported by Bechterew: muscle afferents end in the (rostral) area 3a, as Phillips, Powell and Wiesendanger (1971) have demonstrated in the baboon.

Bechterew had been rather vague when he defined the place of his posterior lesion as lying 'above the beginning of the fossa Sylvii within the third or fourth primitive gyrus'. When in 1941 Adrian described a second somatosensory cortex (the S2 of Woolsey, 1943) he recorded responses to peripheral stimuli in the cat's cortex behind the anterior ectosylvian sulcus near the base of the brain (*see* fig. 1 and Adrian's fig. 1). This would be also within the space outlined by Bechterew.

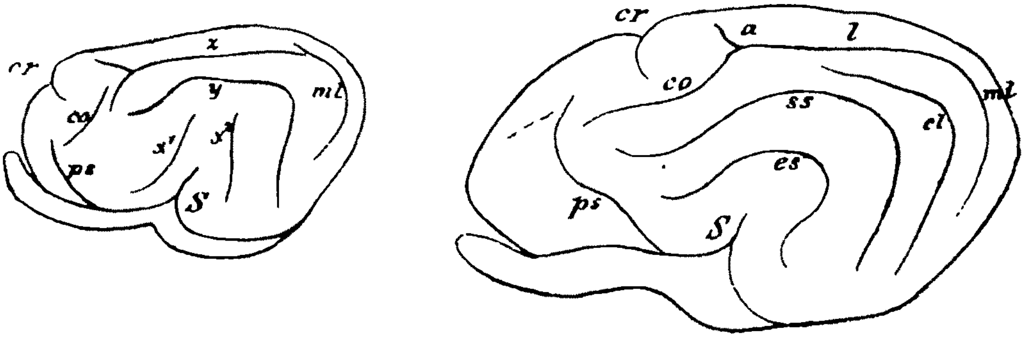


FIG. 1 showing lateral convexity of the brain of the cat (left) and the dog (right). Cr=sulcus cruciatus, Co=s. coronalis, a=s. ansatius, ps=s. praesylvius, ss (y)=s suprasylvius, es (x^1, x^2)=s. ectosylvius anterior and posterior. S.=s. pseudosylvius (there exists no true Sylvian fissure in carnivores). (Reproduced by permission of the Gustav Fischer Verlag, Jena, from figs 1 and 2 of Ziehen (1890)

Adrian, however, obtained responses to both tactile and pressure stimuli, whereas Bechterew, who investigated his dogs after recovery from anæsthesia, was very positive that only positional sensation had been lost. Therefore, there is some justification in assuming that Bechterew's posterior lesion was not identical with Adrian's second somatosensory cortex, but placed within a more dorsal area which would correspond to the caudal portion of the primate's postrolandic cortex and still be within the limits set by Bechterew.

Apart from mentioning the fossa Sylvii, Bechterew did not name any sulci knowledge of which was rather uncertain at this early period. In carnivores, the Sylvian fissure of higher species is not yet developed; instead they have a 'pseudosylvian' sulcus (Elliot Smith, 1902) which runs an almost vertical course. It is quite possible that when he spoke of the beginning of the fossa Sylvii, Bechterew meant the anterior ectosylvian sulcus above which he placed his posterior lesion.

For reasons we can only guess, however, Bechterew did not maintain his views. In 1885 he began his long collaboration with Flechsig who in the same year briefly spoke of a continuation of the medial lemniscus to the cerebral cortex—his 'Rindenschleife'. In his later paper with Hösel (1890) Flechsig regarded both Rolandic convolutions as the 'central organ of the posterior spinal tracts'. Bechterew may also have been swayed by the growing number of workers of repute (including Luciani, Dana, Starr and Horsley) who from the middle 1880's onwards concluded that both Rolandic convolutions contained mixed sensory and motor centres.

The Homologue of the Primate's Rolandic Sulcus in Carnivores

In his Croonian lecture, Ferrier (1890) expressed his belief that the sulcus cruciatus was the homologue in carnivores of the primate's central sulcus and not the coronal sulcus, as Owen (1868), Pansch (1875), Meynert (1877) and Turner (1890) had assumed. Ferrier had held this view since 1876, and he was strongly supported by the conclusions of Kükenthal and Ziehen (1889) and Ziehen (1890, *see* my fig. 1).

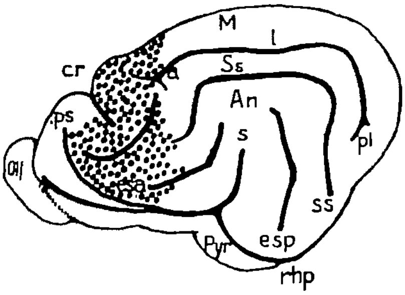


FIG. 2 Lateral convexity of the cat's brain. Punctate region indicates extent of the 'gigantopyramidal cell' type. Description in text. (Reproduced from fig. 22 of Brodmann, 1905).

Using his cytoarchitectonic method, Brodmann (1905, p. 117, *see* his fig. 22, my fig. 2) concluded that in all carnivores the area gigantopyramidalis is found in the posterior part of the sigmoid gyrus, but in some subspecies (for example, cat, dog and wolf) it may also occupy most of its anterior portion. This excludes the sulcus cruciatus as a possible homologue in carnivores of the primate's sulcus centralis. Modern opinion (Ariëns-Kappers, Huber and Crosby, 1960, Vol. **3**, p. 1532) altogether denies that the cruciate sulcus has an equivalent structure in the primate's brain. On the other hand Brodmann (1905, figs. 20 and 22) has shown that the coronal sulcus only partially constitutes a caudal border to the gigantopyramidal cortex which dorsally ends well in front of the ansate sulcus and ventrally penetrates by at least a third into the gyrus suprasylvius anterior (or gyrus coronalis, a name given by Langley (1883) and used by Brodmann and some other workers). Brodmann believed no single sulcus in lower species serves as a homologue of the primate's central sulcus (which, in turn, however, is not a single structure but formed by several components). Brodmann's findings agree with the earlier ones of Hitzig (1874, p. 136, fig. 10) who, in the dog, suggested a combination of two different sulci, both named R. Elliot-Smith also proposed a (now unacceptable) combination of the coronal and cruciate sulci. More recently Ariëns-Kappers and his associates (1960) favoured a combination of the coronal sulcus and sulcus ansatus as a likely homologue in carnivores and other lower species of the central sulcus.

Brodmann maintained his findings and conclusions in his book of 1909 (*see* his fig. 104, p. 183); they were confirmed and amplified by, among others, Gurewitch and Bychowsky (1928), Filimonoff (1928), McKibben and Wheelis (1932) and by Garol (1942*a*). The cytoarchitecture of the somatosensory cortex was found within the anterior suprasylvian (sive coronal) gyrus extending dorsally for some distance into the posterior sigmoid nucleus (*see* Brodmann, 1909, p. 183, fig. 104). Garol (1942*b*) tried in the cat's brain to outline its extent by means of the strychnine method, but as we have seen, recording of cortical responses to peripheral stimuli has proved superior (for example, Adrian, 1941; Hamuy, Bromiley and Woolsey, 1956; *see* the latter authors' fig. 2 which agrees fairly well with Brodmann's (1909) anatomical description and fig. 104).

Gurewitch and Bychowsky, Filimonoff, as well as more recently, Kreiner (1964) have suggested a *postcruciate sulcus* as the homologue in carnivores of the primate's central sulcus. However, this structure is very inconstant; it is shown neither in the illustrations of Brodmann nor in those of Hamuy *et al.* (1956) and Ariëns-Kappers *et al.* (1960).

It was necessary to dwell at some length upon these problems of comparative neuroanatomy because they not only help to understand the experiments and conclusions of Bechterew, but also were at the root of many controversies during the period which has been reviewed in this paper.

SUMMARY

A brief account has been given of the events during the last quarter of the nineteenth century which led to the concept of the sensorimotor cortex. An early review by Frederick Mott has served as a useful guide. Particular attention has been paid to two early startlingly prescient papers by W. Bechterew. Since, however, Bechterew changed his views in subsequent publications, he forfeited a major claim for priority, and his early papers were forgotten.

ACKNOWLEDGEMENTS

I am greatly indebted to Dr. Peter Nathan and Dr. Raymond Hierons for their valuable criticisms and helpful advice, to Dr. Nina Meyer who substantially improved the style of the paper, and to Mrs. Ursula Baker for her care in preparing the manuscript. My thanks are also due to Gustav Fischer Verlag for permission to reproduce fig. 1 (detail is given in the references).

REFERENCES

Adrian, E. A. (1941) Afferent discharges to the cerebral cortex from peripheral sense organs. *Journal of Physiology, London*, **100**, 159–191.

Ariens-Kappers, C. U., Huber, G. C. and Crosby, E. C. (1960) *The Comparative Anatomy of the Nervous System of Vertebrates, Including Man*. New York. Hafner, Vol. 3, p. 1532.

BAIN, A. (1864) *The Senses and the Intellect.* 2nd Edition. (First published 1855). London: Longman and Green, pp. 92-95.

BASTIAN, H. C. (1887) 'The muscular sense', its nature and cortical localization. *Brain*, **10**, 1-137.

BECHTEREW, W. (1883) Über die Lokalisation der Hautsensibilität (Tast- und Schmerzempfindungen) und des Muskelsinnes an der Oberfläche der Grosshirnrindenhemispheren. *Neurologisches Centralblatt*, **2**, 409-414.

—— (1885) Wie sind die Erscheinungen zu verstehen, die nach Zerstörung des motorischen Rindenfeldes an Thieren auftreten? *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere*, **35**, 137-145.

—— (1899) *Die Leitungsbahnen im Gehirn und Rückenmark.* (First published 1894). Leipzig: Georgi.

—— (1911) *Die Funktionen der Nervencentra.* Jena: Fischer, Vol. 3.

BEEVOR, C. E. and HORSLEY, V. A. H. (1891) A record of the results obtained by electrical excitation of the so-called motor cortex and internal capsule in an orang-utang (*Simia satyrus*). Philosophical Transactions **181B**, 129-158.

BONIN, G. VON (1960) *Some Papers on the Cerebral Cortex.* Springfield: Thomas.

BRODMANN, K. (1905) Beiträge zur histologischen Lokalisation der Grosshirnrinde. 4, Mitteilung: Der Riesenpyramidentypus und sein Verhalten zu den Furchen bei den Karnivoren. *Journal für Psychologie und Neurologie*, **6**, 108-120.

—— (1909) *Vergleichende Lokalisationslehre der Grosshirnrinde.* Leipzig: Barth. (Quoted from 2nd unchanged Edition, 1925).

CARVILLE, C. and DURET, H. (1875) Sur les fonctions des hémisphères cérébraux. *Archives de Physiologie*, Second Series, **2**, 352-491.

CLARKE, E. C. and O'MALLEY, C. D. (1968) *The Human Brain and Spinal Cord.* Berkeley and Los Angeles: University of California Press, p. 515.

CUSHING, H. (1909) A note upon the faradic stimulation of the postcentral gyrus in conscious patients. *Brain*, **32**, 44-53.

DANA, C. L. (1888) The cortical localization of the cutaneous sensations. *Journal of Nervous and Mental Disease*, **13**, 650-684.

ELLIOT SMITH, G. (1902) On the homologies of the cerebral sulci. *Journal of Anatomy and Physiology, London*, **36**, 309-319.

FERRIER, D. (1886) *The Functions of the Brain.* 2nd Edition. London: Smith and Elder (First Edition, 1876).

—— (1890) *The Croonian Lectures on Cerebral Localisation.* London: Smith and Elder.

—— and YEO, G. F. (1884) A record of experiments on the effects of lesions of different regions of the cerebral hemispheres. *Philosophical Transactions*, **175**, 479-564.

FILIMONOFF, I. N. (1928) Über die Varianten der Hirnfurchen des Hundes. *Journal für Psychologie und Neurologie, Leipzig*, **36**, 22-43.

FLECHSIG, P. E. (1885) Ueber die Verbindungen der Hinterstränge mit dem Gehirn. *Neurologisches Centralblatt*, **4**, 97-100; 356-359.

FLECHSIG, P. E. and HÖSEL, O. (1890) Die Centralwindungen ein Centralorgan der Hinterstränge. *Neurologisches Centralblatt*, **9**, 417–419.

GAROL, H. W. (1942*a*) The 'motor' cortex of the cat. *Journal of Neuropathology and Experimental Neurology*, **1**, 139–145.

—— (1942*b*) Cortical origin and distribution of corpus callosum and anterior commissure in the cat. *Journal of Neuropathology and Experimental Neurology*, **1**, 422–429.

GRÜNBAUM, A. S. F. and SHERRINGTON, C. S. (1902) Observations on the physiology of the cerebral cortex of some of the higher apes. (Preliminary Communication), *Proceedings of the Royal Society*, **69**, 206–209.

—— —— (1903) Observations on the physiology of the cerebral cortex of the anthropoid apes. *Proceedings of the Royal Society*, **72**, 152–155.

GUREWITCH, M. and BYCHOWSKY, G. (1928) Zur Architektonik der Hirnrinde (Isocortex) des Hundes. *Journal für Psychologie und Neurologie, Leipzig*, **35**, 283–300.

HAMUY, T. P., BROMILEY, R. B. and WOOLSEY, C. N. (1956) Somatic afferent areas I and II of dog's cerebral cortex. *Journal of Neurophysiology*, **19**, 485–499.

HITZIG, E. (1874) *Untersuchungen über das Gehirn*. Berlin: Hirschwald.

—— (1877) *Über den Heutigen Stand der Frage von der Lokalisation im Grosshirn*. Volkmann's Sammlung No. 112. Leipzig. (quoted from F. W. Mott, 1894).

HORSLEY, V. A. H. (1909) The function of the so-called motor area of the brain (The Linacre Lecture). *British Medical Journal*, **2**, 125–132.

—— and SCHÄFER, E. A. (1888) A record of experiments upon the functions of the cerebral cortex. *Philosophical Transactions*, **179B**, 1–45.

JACKSON, J. Hughlings (1881) On some implications of dissolution of the nervous system. Med. Pres. & Circul. **2**, 411. Reproduced in: *Selected Writings of John Hughlings Jackson*. (1932) Edited by J. Taylor. London: Hodder and Stoughton, Vol. **2**, pp. 29–44.

—— (1884) Evolution and dissolution of the nervous system. In: *Selected Writings of J. Hughlings Jackson* (1932) Edited by J. Taylor. London: Hodder and Stoughton, Vol. 2, pp. 45–75.

—— (1890) The Lumleian Lectures on convulsive seizures. *British Medical Journal*, **1**, 703–707; 765–771; 821–827.

—— (1898) Remarks on the relations of different divisions of the central nervous system to one another and to parts of the body. *British Medical Journal*, **1**, 65–69.

JAKOVLEV, P. I. (1970) Vladimir Bekhterev. In: *The Founders of Neurology*. 2nd Edition. Edited by W. Haymaker and F. Schiller. Springfield: Thomas, pp. 167–171.

JONES, E. G. (1972) The development of the 'muscular sense' concept during the nineteenth century and the work of H. Charlton Bastian. *Journal of the History of Medicine and Allied Sciences*, **27**, 298–311.

—— and POWELL, T. P. S. (1969) Connexions of the somatic sensory cortex of the Rhesus monkey. I. Ipsilateral cortical connexions. *Brain*, **92**, 477–502.

KREINER, J. (1964) Myeloarchitectonics of the sensory-motor cortex in dog. *Journal of Comparative Neurology*, **122**, 181–200.

KÜKENTHAL, W. and ZIEHEN, T. (1889) Über das Centralnervensystem der Cetaceen nebst Untersuchungen über die vergleichende Anatomie des Gehirns bei Placentalien. *Denkschriften der Medizinisch-naturwissenschaftlichen Gesellschaft zu Jena*, **3**, (1), 80–198.

LANGLEY, J. N. (1883) The structure of the dog's brain. *Journal of Physiology, London*, **4**, 248–285.

LEYTON, A. S. F. and SHERRINGTON, C. S. (1917) Observations on the excitable cortex of the chimpanzee, orang-utan and gorilla. *Quarterly Journal of Experimental Physiology*, **11**, 135–222.

LUCIANI, L. (1884) On the sensorial localisations in the cortex cerebri. *Brain*, **7**, 145–160.

—— and SEPPILI, G. (1885) *Le Localizzazioni Funzionali del Cervello*. Napoli: Vallardi.

—— and TAMBURINI, A. (1878) Ricerche sperimentali sui centri psico-motori corticali. (Quoted from critical digest by A. Rabagliati, *Brain*, **1**, 529–544).

McKIBBEN, P. S. and WHEELIS, D. R. (1932) Experiments on the motor cortex of the cat *Journal of Comparative Neurology*, **56**, 373–389.

MEYNERT, T. (1877) Die Windungen der convexen Oberfläche des Vorderhirnes bei Menschen, Affen und Raubthieren. *Archiv für Psychiatrie und Nervenkrankheiten*, **7**, 257–286.

MOTT, F. W. (1894) The sensory motor functions of the central convolutions of the cerebral cortex. *Journal of Physiology, London*, **15**, 464–487.

MUNK, H. (1890) *Ueber die Functionen der Grosshirnrinde: Gesammelte Mitteilungen mit Anmerkungen*. 2nd Edition. Berlin: Hirschwald. (First Edition, 1881).

NOTHNAGEL, H. (1873) Experimentelle Untersuchungen ueber die Functionen des Gehirns. *Virchows Archiv für pathologische Anatomie und Physiologie und für Klinische Medizin*, **57**, 184–214.

OWEN, R. (1868) *The Comparative Anatomy and Physiology of the Vertebrates*. London: Longman and Green, Vol. 3.

PANSCH, A. (1875) Über gleichwertige Regionen am Grosshirn der Carnivoren und der Primaten. *Zentralblatt für die medizinischen Wissenschaften*, **13**, 641–645.

PENFIELD, W. and RASMUSSEN, T. (1950) *The Cerebral Cortex of Man*. New York: Macmillan.

PHILLIPS, C. G., POWELL, T. P. S. and WIESENDANGER, M. (1971) Projection from low-threshold muscle afferents of hand and forearm to area 3a of baboon's cortex. *Journal of Physiology, London*, **217**, 419–446.

POWELL, T. P. S. and MOUNTCASTLE, V. G. (1959) Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: a correlation of findings obtained in a single unit analysis with cytoarchitecture. *Bulletin of the Johns Hopkins Hospital*, **105**, 133–162.

SCHÄFER, E. A. (1898) On the alleged sensory functions of the motor cortex cerebri. *Journal of Physiology, London*, **23**, 310–314.

—— (1900) *Textbook of Physiology*. Edinburgh and London: Pentland, Vol. **2**, pp. 697–782.

SCHIFF, M. (1875) Untersuchungen über die motorischen Functionen des Grosshirns. *Archiv für experimentelle Pathologie und Pharmakologie*, **3**, 171–179.

STARR, A. (1884) The sensory tract in the central nervous system. *Journal of Nervous and Mental Disease*, **11**, 327–407.

TURNER, W. (1890) The convolutions of the brain: a study in comparative anatomy. *Journal of Anatomy and Physiology, London,* **25,** 105–153.

VOGT, C. and VOGT, O. (1907) Zur Kenntnis der electrisch erregbaren Hirnrindengebiete bei den Säugetieren. *Journal für Psychologie und Neurologie, Leipzig,* **8,** 277–454.

WOOLSEY, C. N. (1943) 'Second' somatic receiving areas in the cerebral cortex of cat, dog and monkey. *Federation Proceedings,* **2,** 55–56.

ZIEHEN, T. (1890) Zur vergleichenden Anatomie der Hirnwindungen mit spezieller Berücksichtigung der Gehirne von Ursus maritimus und Trichechus rosmarus. *Anatomischer Anzeiger,* **5,** 692–709.

(*Received June 22, 1978*)

Brain (1978), **101**, 687-700

EPILEPTIC BRAIN DAMAGE

THE ROLE OF SYSTEMIC FACTORS THAT MODIFY CEREBRAL ENERGY METABOLISM

by G. BLENNOW, J. B. BRIERLEY, B. S. MELDRUM *and* B. K. SIESJÖ

(From the MRC Cerebral Metabolism Group, E-Blocket, University Hospital, Lund, Sweden; The Brain Hypoxia Group, The MRC Laboratories, Carshalton, Surrey, U.K. and the Department of Neurology, Institute of Psychiatry, London)

INTRODUCTION

FOLLOWING prolonged epileptic seizures in animals or man, loss of nerve cells and gliosis may be found in the cerebellum, hippocampus, amygdala, cerebral cortex or thalamus (*see* Corsellis and Meldrum, 1976). Initial suggestions (Spielmeyer, 1927; Scholz, 1959) that systemic hypoxia or arterial spasm (or compression) were responsible have not been substantiated by subsequent clinical or experimental studies. Observations on prolonged seizures induced in baboons by bicuculline (Meldrum and Horton, 1973; Meldrum and Brierley, 1973) have led to the suggestion that secondary physiological changes occurring late in prolonged seizures (including arterial hypotension, hypoxia, hypoglycæmia and hyperthermia) contribute to the causation of brain damage. However, there is also evidence that seizure discharges in the brain can induce ischæmic neuronal changes in the absence of secondary systemic disturbances likely to impair cerebral energy metabolism (Meldrum, Vigouroux and Brierley, 1973).

In the rat, under light nitrous oxide anæsthesia with peripheral neuromuscular blockade, it is possible to induce prolonged seizures with bicuculline and to monitor and control appropriate physiological variables over a period of two hours (Chapman, Meldrum and Siesjö, 1977). We have used this model to evaluate the potential contribution of different systemic factors by varying each one in isolation. The factors that we have evaluated are arterial hypotension, arterial hypoxia, hypoglycæmia and hyperthermia. The brains have been fixed by perfusion directly after the seizure period so that the early stages of ischæmic cell change (Brown and Brierley, 1968) can be evaluated by light microscopy. In parallel experiments, groups of rats maintained under identical physiological conditions have undergone seizures of the same duration, but terminating with rapid *in situ* freezing of the brain to permit estimations of labile phosphates, glycolytic metabolites, citric acid cycle intermediates and associated amino acids (Chapman *et al.*, 1977; Blennow, Nilsson and Siesjö, 1977, 1978*c*; Blennow, Folbergrová, Nilsson and Siesjö, 1978*b*). Similar matching studies of cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}) and glucose have been undertaken (Meldrum and Nilsson, 1976; Borgström, Chapman and Siesjö, 1976; Blennow *et al.*, 1977, 1978*b*, *c*). These results, which are reported independently, facilitate the interpretation of the present experiments.

MATERIALS AND METHODS

Operative Procedure

Male Wistar rats (285–410 g) were allowed free access to water and food pellets until anæsthesia was induced with 3 per cent halothane (except for the Hypoglycæmia Group in which food pellets were withdrawn twenty-four hours earlier). Animals were tracheotomized, immobilized with tubocurarine chloride (1 mg/kg), heparinized (100 IU/kg), and artificially ventilated with 70 per cent nitrous oxide and 30 per cent oxygen. Femoral venous and arterial cannulæ were inserted. Arterial pressure, the electroencephalogram (from platinum needle electrodes, or gold-plated bolts inserted in the skull) and, when necessary, the electrocardiogram, were recorded polygraphically. Rectal temperature was maintained close to 37° C by external heating. Halothane was withdrawn and the animals were stabilized on N_2O/O_2 for 15–20 min. Prior to bicuculline injection, arterial blood (1–3 ml) was slowly withdrawn so as to reduce mean arterial pressure from 150–165 mmHg to 120–140 mmHg (this was to diminish the severity of the early ictal hypertension). Bicuculline hydrochloride (Sigma Chemical Co.) dissolved in 0·1 M HCl and brought to pH 4–5 with 1 N NaOH, was injected intravenously in a dose of 1·2 mg/kg. Arterial P_{O_2}, P_{CO_2} and pH were determined with microelectrodes at 37° C (Eschweiler and Co., Kiel, and Radiometer, Copenhagen) and corrected for body temperature. In a few experiments the EEG seizure appeared to decline in intensity and a second injection of bicuculline was given. Some animals also received sodium bicarbonate (0·3–0·5 ml of a 0·6 M soln) intravenously

The following procedures were adopted to give the required groups.

Standard seizure (13 rats). EEG seizure activity continuing uninterrupted for two hours, with mean arterial pressure maintained above 120 mmHg by infusion of heparinized donor blood, arterial oxygen tension generally above 100 mmHg, arterial CO_2 tension 30–40 mmHg, rectal temperature close to 37° C.

Arterial hypotension was induced in two groups: (1) *Moderate* (12 rats), as for Standard Seizure except that mean arterial pressure was lowered by bleeding 5–25 min after onset of seizure, and subsequently maintained at 70–75 mmHg. (Sodium bicarbonate was given to 5 rats); (2) *Severe* (6 rats), as for Standard Seizure except that the mean arterial pressure was brought to 50 mmHg after 15–25 min and subsequently maintained at or just below this level.

Hypoxia (7 rats) The percentage of oxygen in the inspired gas mixture was reduced to give an arterial P_{O_2} close to 50 mmHg, at approximately 30 min after the bicuculline injection. The N_2O concentration was maintained at 70 per cent by admixture of N_2. (Four rats received a second injection of bicuculline. All 7 rats received sodium bicarbonate).

Hypoglycæmia (6 rats). Rats were provided with water but no food pellets for 24 h before the bicuculline injection. In such fasted rats, continuous seizure activity leads to a progressive reduction in blood glucose concentrations (Blennow *et al.*, 1978*b*).

Hyperthermia (7 rats). By means of external heating the body temperature was raised so that it reached close to 40° C after about 30 min. This temperature was maintained for the rest of the experimental period. (Four rats received sodium bicarbonate solution).

Fixation. At the end of the 2 h period (with seizure activity and mechanical ventilation with N_2O/O_2 still continuing), perventricular-aortic perfusion of the brain was performed. Heparin and a 30–60 s washout with physiological saline solution preceded perfusion with a formalin/acetic acid/methanol mixture (1,1,8 by volume) at systolic blood pressure for 20 min. Subsequently the brains were numerically coded and blocks from forebrain, brain-stem and cerebellum were embedded in paraffin Sections were stained with cresyl violet and Lugol fast blue and with hæmatoxylin and eosin Neuropathological assessment (by J.B.B.) was performed 'blind'.

RESULTS

Cardiorespiratory Physiology

In all six experimental groups, the initial physiological changes following bicuculline injection conformed to the description given by Meldrum and Nilsson (1976) and Chapman *et al.* (1977). A rise in mean arterial blood pressure to 180–210 mmHg was consistently observed. It declined from 5–15 min after onset of seizure and its subsequent level was governed by experimental manipulations.

Mean values for the key physiological variables, determined (a) after the selective manipulations have taken effect, and (b) at the end of the experimental period, are summarized in Table 1. This shows the uniformity and stability achieved in the Standard 2 h seizure Group. In the Moderate and Severe Hypotension Groups the required arterial pressures were closely held. Hypotension produced a fall in arterial CO_2 tension (with unchanged mechanical ventilation) and a marked acidosis. Arterial pressure was slightly lower in the Hypoxia Group than in the Standard Group.

In the Hypoglycæmia Group the arterial glucose concentration prior to bicuculline injection, although not 'hypoglycæmic', was markedly lower ($6{\cdot}2 \pm 0{\cdot}2\,\mu$ mol/g, Chapman *et al.*, 1977). Hypoglycæmic levels were reached in approximately 30 min ($3{\cdot}1 \pm 0{\cdot}2\ \mu$ moles/g) the time course is shown in detail in Blennow *et al.*, 1978*b*. The final value was similar ($3{\cdot}3 \pm 0{\cdot}2\ \mu$ moles/g).

In parallel hypoglycæmia experiments we (Blennow *et al.*, 1978*b*) observed initial concentrations of ketone bodies in the blood (β-hydroxybutyrate, 1·93 μ mol.g^{-1}; acetoacetate, 0·630 μ mol.g^{-1}) similar to those previously described in rats starved for 24 hours (Ruderman, Ross, Berger and Goodman, 1974). During the seizure, β-hydroxybutyrate concentration fell progressively (to 1·02 μ mol.g^{-1} at 20 min and 0·55 μ mol.g^{-1} at 120 min). Acetoacetate fell rapidly to 0·235 μ mol.g^{-1} (at 5 min) and to 0·088 μ mol.g^{-1} while the EEG showed single spikes.

The total volume of donor blood infused to maintain an arterial pressure above 120 mmHg was between 8 and 12 ml. This significantly increased the hæmoglobin content (for example, in the Hypoglycæmic Group, from 134±4 to 168±7 g/l).

EEG Changes

Standard group. Onset of the seizure was indicated by rapid irregular spikes, becoming of greater amplitude and rhythmicity, slowing from 10 Hz over 2 min. Subsequently, bursts of rapid, irregular spikes were interspersed with isolated

TABLE 1. PHYSIOLOGICAL VARIABLES DURING BICUCULLINE-INDUCED SEIZURES IN SIX GROUPS OF RATS

	Mean arterial pressure (mmHg)		*Arterial P_{O_2} (mmHg)*		*Arterial P_{CO_2} (mmHg)*		*Arterial pH*		*Temperature ° C*	
Group	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Standard (n=13)	128±2	123±2	128± 8	130± 8	39±1	37±1	6·952±0·000	7·100±0·031	37·2±0·1	37·2±0·1
Moderate hypotension (n=12)	*71±1*	*73±1*	144± 8	134± 6	26±2**	33±2	6·877±0·044	6·872±0·044**	36·8±0·2	37·1±0·1
Severe hypotension (n=6)	*50±0*	*48±1*	143±14	135±11	26±3**	30±3*	6·893±0·031	6·831±0·000**	37·3±0·4	36·7±0·3
Hypoxia (n=7)	119±4*	114±4*	*51± 2*	*45± 4*	35±3	39±2	6·934±0·000	7 040±0·044	36·7±0·1*	37·1±0·1
Hypoglycæmia (n=6)	132±2	128±3	169± 6**	137± 8	32±2**	39±1	6·980±0·000	7·019±0·000	37·1±0·2	36·9±0·3
Hyperthermia (n=7)	125±7	114±4*	154±14	144±16	42±2	38±2	6·943±0·044	7·172±0·083	*40·1±0·1*	*40·1±0·1*

A=values determined at the end of manipulations creating the defined conditions (i.e. 30–60 min of seizure activity). B=value determined just before the end of the seizure period (i.e. 110–120 min of seizure activity). Values are mean±SEM, * $P<0·05$; ** $P<0·01$ (Student's t test, compared with corresponding Standard Group. Values in italics (defining the Groups) $P<0·001$.

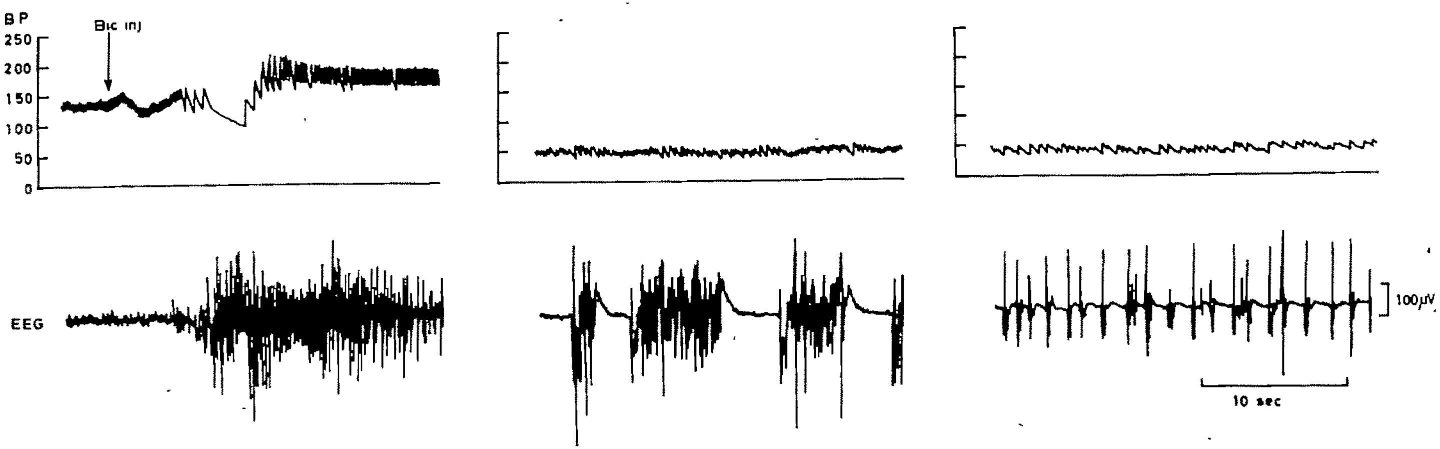


FIG. 1 Simultaneous records of arterial blood pressure in mmHg (BP) and of electrical activity from skull electrodes (EEG) in a rat in the Severe Hypotension Group *Left hand* traces show onset of electrocortical seizure a few seconds after the intravenous injection of bicuculline, 1·2 mg/kg (Bic inj.), accompanied by severe bradycardia and an increase in arterial pressure. *Middle traces* show an EEG pattern with bursts of spikes when the mean arterial pressure is 50 mmHg (25 min after onset of seizure). *Right hand traces* show isolated spikes on the EEG record when mean arterial pressure is just below 50 mmHg (71 min after onset of seizure).

spikes. Bursts lasted 2–20 s, with brief silent periods or a few spikes or polyspikes and waves separating them (*see* fig. 1, and Chapman *et al.*, 1977).

Moderate arterial hypotension. EEG seizure activity was similar to that in the normotension group.

Severe arterial hypotension. When the mean arterial pressure fell initially to 50 mmHg, longer episodes (30–120 s) of isolated single spikes or of polyspike and wave patterns tended to intersperse the bursts of fast spikes. This was more marked if the mean arterial pressure fell to around 45 mmHg; rapidly recurrent bursts of fast spikes returned if the mean pressure rose above 50 mmHg.

Hypoxia. A transition to brief periods with isolated single spikes was seen at variable intervals after attainment of the required level of arterial hypoxia. In four experiments, such periods were followed by absence of seizure activity; injection of bicuculline (1 mg/kg) restored EEG seizure activity, with a single spike pattern predominating.

Hypoglycæmia. At approximately 30 min after onset of seizure, the EEG showed a transition from recurrent bursts of rapid spikes to isolated spikes (repeated roughly every 1–5 s, with occasional rare bursts of spikes). A further bicuculline injection generally produced one or two bursts of rapid spikes, then continuation of the single spike pattern.

Hyperthermia. At about 90 min after seizure onset (that is, after 1 h at approximately 40° C) there was a tendency for the burst-suppression pattern to be replaced by isolated spikes (in the 2 most marked cases only single spikes were seen during the last 30 min of seizure activity).

Neuropathological Alterations

Standard group. The principal neuronal change (observed in 11 out of 13 brains, *see* Table 2) was ischæmic cell change, or the transitional stage from microvacuolation to ischæmic cell change (Brown and Brierley, 1968). This was seen most frequently in the neocortex, predominantly involving smaller neurons in the outer layers (1–3), but occasionally also involving the deeper cortical layers (5 and 6). In general only a small proportion of neurons showed such changes; these occurred in a diffuse fashion, symmetrically, and at both anterior and posterior levels in the cortex.

In the hippocampus similar neuronal changes were seen involving, in both hemispheres, a small number of neurons in the Sommer sector (h_1) and, in 3 animals only, the endfolium (h_{3-5}).

In the striatum 3 animals showed ischæmic changes involving a few scattered small pleomorphic neurons.

In the thalamus scattered ischæmic neurons were found in 4 animals occurring usually with a focal (perivascular) distribution.

The cerebellum and brain-stem showed no neuronal changes.

Moderate hypotension. In one rat scattered neurons in the outer layers of the cortex showed ischæmic cell change; other brain areas were normal.

Severe hypotension. In 5 animals the cortex showed ischæmic neuronal changes similar in kind and distribution to those observed in the Standard Group. In one animal microvacuolation was seen in nearly all the neurons in the endfolium in one hemisphere; otherwise hippocampal damage was not seen. In one brain scattered neurons in the striatum showed early ischæmic cell change.

Hypoxia. The 7 brains in this group showed no clear evidence of ischæmic cell change.

Hypoglycæmia. In 2 brains a few neurons in the outer cortical layers showed microvacuolation and early ischæmic neuronal change. Other brain areas were normal.

Hyperthermia. In all 7 animals in this group ischæmic cell change was observed in scattered neurons in the outer cortical layers. In contrast to the Standard Group the changes indicated a more advanced stage of ischæmic cell change; in all 7 brains 'incrustations' (Brown and Brierley, 1968) were a prominent feature. In the Sommer sector of the hippocampus ischæmic cell change (but without incrustations) was seen rather than the transition from microvacuolation to ischæmic cell change seen commonly in the Standard Group. In one animal scattered neurons in the striatum showed ischæmic cell change.

Table 2. Number of Animals Showing Microvacuolation and/or Ischæmic Cell Change in the Brain after 2 h Seizure Activity under Various Physiological Conditions

	No. in group	*Region*					*Total*
		Cortex	*Hippocampus*			*Striatum*	
			h_1	h_{3-5}	*total*		
Standard	13	11	9	3	9	3	11
Moderate hypotension	12	1	0	0	0	0	1**
Severe hypotension	6	5	0	1	1	1	5
Hypoxia	7	0	0	0	0	0	0**
Hypoglycæmia	6	2	0	0	0	0	2**
Hyperthermia	7	7	6	0	6	1	7

* or ** = significantly different from the *Standard* Group at the 5 per cent or 1 per cent level (Fisher's exact probability test).

DISCUSSION

The acute pathology observed here, microvacuolation and ischæmic cell change, is similar in cellular morphology and regional cerebral distribution to that observed in baboons after three hours or more of seizure activity with paralysis and mechanical ventilation (Meldrum *et al.*, 1973).

Both the rats and the baboons show a predominance of cerebral cortical and hippocampal damage (Meldrum and Brierley, 1973). Microvacuolation (which is the appearance under the light microscope of cytoplasm containing grossly swollen and disorganized mitochondria, Brown and Brierley, 1973) and ischæmic cell change are the result of a variety of stresses which have as a common feature the disruption of cellular energy metabolism. Such manipulations include arterial hypotension, hypoglycæmia, systemic hypoxia, cerebral oligæmia or ischæmia (Brierley, 1976).

As seizure activity augments cerebral energy consumption (as evaluated by measurements of oxygen and glucose consumption, or of metabolic intermediates) a failure of energy supply to keep pace with energy utilization would seem likely to be an important factor contributing to acute epileptic brain damage. However, our observation that in a physiologically controlled situation, ischæmic cell change is less severe in the presence of a moderate reduction of cerebral oxygen availability or hypoglycæmia, argues against such a mechanism operating in a simple manner. Clearly factors other than energy charge need to be considered as causes of ischæmic neuronal change following sustained seizure activity.

A raised intracellular lactate concentration is thought by various authors to be toxic or lethal (*see* Wasterlain, 1974). Myers (1977) has suggested that lactate accumulation in the brain is responsible for the cerebral œdema and necrosis occurring in glucose pretreated rhesus monkeys subjected to 14 minutes of cardiac arrest (but not occurring when the animals are food- and glucose-deprived). From a comparison of various hypoxic and ischæmic stresses, Myers (1977) concludes that a brain lactate concentration exceeding 25 μmol/g will produce widespread tissue destruction. The lactate measurements in Table 3, collected from parallel studies (Blennow *et al.*, 1977; Blennow *et al.*, 1978*a*, 1978*b*) show that, in status epilepticus, the different acute neuropathological outcomes cannot be attributed simply to different lactate concentrations. For example, lesions were observed in the *Standard* group at lower lactate concentrations than those observed in the *Moderate Hypotension* and the *Hypoxia* groups, and yet, animals in the latter groups showed hardly any lesions. It is conceivable that lactic acidosis is detrimental only when energy failure is present (*see below*).

Is it possible that physiological factors other than those defining our six groups could be determining the different pathological outcomes?

Blood-brain barrier dysfunction has been shown by leakage of plasma protein-bound dye during bicuculline-induced seizures in rats, and appears to be a consequence of the combination of a high arterial pressure and a reduced cerebrovascular resistance early in the seizure (Johansson and Nilsson, 1977). This will thus occur to the same extent in all six groups, but its later consequences might be slightly different according to the CBF and arterial pressure. Its regional selectivity, however, (principally in the diencephalon and mesencephalon) shows no relationship to the distribution of ischæmic cell change.

TABLE 3. LABILE CEREBRAL METABOLITES IN CEREBRAL CORTEX OF CONTROL RATS AND AFTER 2 H OF SUSTAINED BICUCULLINE-INDUCED EPILEPTIC SEIZURES IN STANDARD ANIMALS (NORMOXIC, NORMOTENSIVE, NORMOTHERMIC) AND IN ANIMALS WITH MODERATE HYPOTENSION (MEAN ARTERIAL BLOOD PRESSURE 75 mmHg), HYPOXIA Pa_{O_2} 44·2±3·5 mmHg), HYPOGLYCÆMIA OR HYPERTHERMIA (BODY TEMPERATURE 40·3±0·1° C).

	Phosphocreatine	*ATP*	*EC+*	*Lactate*	*La/Py*
Control (n=12)	4·47±0·08	3·02±0·02	0·947±0·000	1·42±0·10	11 5±0·6
Standard (n=5)	3·39±0·27	2·94±0·03	0·937±0·002	9·14±1 76	52·6±7·5
Hypotension (n=6)	2·65±0·10*	2·94±0·04	0·933±0·002	16·06±1·05**	92·5±4·8**
Hypoxia (n=6)	2·61±0 30	2·80±0·06	0·931±0·004	23·22±2·03***	143 9±23·1**
Hypoglycæmia (n=3)	3·38±0·15	2·33±0·02***	0·913±0·008**	1·31±0·23*	17·6±0 8**
Hyperthermia (n=5)	2·38±0·13**	2·92±0·03	0·933±0·002	17·72±1·55**	95·0±13·3**

Mean±SEM in μmol g^{-1} of wet tissue (Blennow *et al.*, 1977, 1978*a*, *b*, *c*). For statistical evaluation the Hypotension, Hypoxia, Hypoglycæmia and Hyperthermia Groups have been compared with the Standard Group, not the Control Group. * $P<0·05$, ** $P<0·01$, *** $P<0 001$. + EC=adenylate 'energy charge'=

$$\frac{/ATP/+0·5/ADP/}{/ATP/+/ADP/+/AMP/}$$

Intracranial pressure and cerebral venous pressure increases markedly in the initial seizure phase, both in baboons (Meldrum and Horton, 1973) and in rats (Meldrum and Nilsson, 1976) but probably to a comparable extent in all our six groups. Subsequently it falls showing a relationship to the arterial pressure and CBF. A similar reasoning to that given above for blood-brain barrier dysfunction makes it unlikely that venous pressure is critical in the causation of cerebral cortical ischæmic neuronal changes. However, the presence of cortical damage and the absence of hippocampal damage in the Severe Hypotension Group (in which cerebral blood flow, intracranial pressure and cerebral venous pressure would be lowest) draws attention to the possible role of such factors in hippocampal damage. Many previous authors (Morel and Wildi, 1956; Scholz, 1959; McLardy, 1974) have proposed that a local vascular factor is important in the pathogenesis of epileptic damage in the hippocampus, but experimental proof of this is so far lacking.

The *administration of sodium bicarbonate* solution to some rats did not appear to modify the acute neuropathological outcome. Approximately half the animals in the moderate hypotension, and the hyperthermia groups receive bicarbonate solution, but this did not produce any differences within the groups in pathological outcome. Thus it is unlikely that bicarbonate was a major protective factor in the Hypoxia Group.

Energy failure is not a likely explanation for the lesions in the Standard Group since previous studies have revealed that there is only a very small decrease in energy charge (Chapman *et al.*, 1977; Blennow *et al.*, 1977, *see also* Table 3). Furthermore, there was a similar reduction in the Hypoxia Group and the Moderate Hypotension Group in which lesions were virtually absent (*see* Table 3). The results indicate that the enhanced neuronal activity *per se* might be a factor related to the lesions, however probably not the sole one, since there was little or no diminution of the electrical seizure activity in the animals in the Moderate Hypotension Group, and yet these animals showed hardly any lesions.

Is it possible that the high tissue oxygen tension in the Standard Group could come into play as a pathogenetic factor? In all aerobic cells chemical reduction of oxygen gives rise to formation of free radicals that unless quenched can lead to lipid peroxidation and membrane damage (Barber and Bernheim, 1967; Slater, 1972; Fridovich, 1974, 1975; Demopoulos, Flamm, Seligman, Power, Piatronitro and Ransohoff, 1977). There are reasons to believe that free radical formation is proportional to tissue P_{O_2} and to rate of flux in metabolic pathways including the respiratory chain. Direct measurements of tissue P_{O_2} during seizures often reveal an increase (Gurdjian, Webster and Stone, 1947; Caspers and Speckman, 1972) and studies of Jöbsis, O'Connor, Vitak and Wremon (1971) have shown that oxidation of mitochondrial NADH occurs. We may thus propose that in the Standard Group the combination of increased P_{O_2} and enhanced metabolic rate overwhelms the cellular defence against free radicals which leads to oxidative degradation of intracellular membranes.

Reduction of arterial pressure to about 75 mmHg or of P_{O_2} to about 40–50 mmHg should eliminate the surplus of brain oxygen supply brought about by the pronounced increase of cerebral blood flow during uncomplicated seizures (Meldrum and Nilsson, 1976; Blennow *et al.*, 1978*b*, *c*). At this level of moderately reduced cerebral oxygen availability the EEG pattern is unchanged, CMR_{O_2} is upheld at supranormal values, and the energy charge maintained at levels observed in the Standard Group (cf. Table 3). In this situation reduction of tissue P_{O_2} may explain why lesions were less pronounced. The further reduction of oxygen availability associated with severe hypotension is accompanied by a transition into an EEG pattern of single spikes and a CMR_{O_2} below about 150 per cent of control (Blennow *et al.*, 1978*b*). This occurs when the oxygen is virtually completely extracted from the cerebral blood, and at an energy charge of about 0·91. Thus, the neuronal lesions seen in the Severe Hypotension Group could conceivably be ascribed to energy failure combined with abnormal neuronal activity.

Parallel studies during sustained seizures combined with hypoglycæmia (Blennow *et al.*, 1978*b*) show that when the EEG changes into a pattern with isolated single spikes, CMR_{O_2} returns to normal levels, and the cerebral blood flow falls to normal or sub-normal values. The net effect of these changes on cerebral energy metabolism is summarized in Table 3. It can be seen that there was a moderate fall in energy charge almost as pronounced as in the Severe Hypotension Group (*see above* and Blennow *et al.*, 1978*c*). Nevertheless, the corresponding animals in the present investigation were protected from neuronal damage. Conceivably this could be due to the absence of lactic acid accumulation and to a reduction of seizure activity (and metabolic flux) preventing further energy perturbation.

Apparently the further metabolic stress exerted by the hyperthermia (*see* Carlsson, Hägerdal and Siesjö, 1976) exaggerated the neuronal lesions. This finding is therapeutically relevant to the brain damage following prolonged febrile convulsions and hyperthermia occurring in status epilepticus (*see* Corsellis and Meldrum, 1976).

Clearly, the complex relations between cerebral glucose and oxygen availability and neuronal function and metabolism lead to unpredictable consequences for cellular integrity during seizures. The pathogenetic mechanisms leading to lesions remain to be elucidated. However, it seems a distinct possibility that lesions occurring in the absence of overt energy failure are due to increased oxygen tensions and metabolic rate, while those seen at severe reductions in oxygen availability are influenced by failure of cellular energy. In between these extremes of oxygen availability, there appears to be a 'free interval', possibly because the reduction in tissue oxygen tensions curtails oxidative degradation of cell membranes.

Caution should be exercised in drawing conclusions concerning clinical practice from these results. Sustained seizures induced in anæsthetized, paralysed, artificially-ventilated adult rats are not strictly comparable with status epilepticus in adults or children. Our data lend weight to the common clinical objective of early termination of cerebral seizure activity and prevention or reversal of hyperpyrexia. It is probably not justified to predict the influence on outcome of manœuvres modifying blood pressure, blood gases, blood glucose, plasma osmolarity and pH on the basis of this study.

SUMMARY

The possible role of systemic physiological changes (occurring secondarily during status epilepticus) in the causation of epileptic brain damage has been evaluated in rats. Animals were anæsthetized, paralysed and mechanically

ventilated; sustained electrocortical seizure discharges were induced by the intravenous injection of bicuculline, 1·2 mg/kg. After two hours of seizure activity brains were fixed by perfusion for histology.

Physiological variables were maintained within certain limits from the end of the initial seizure phase (approximate duration twenty minutes) until two hours after onset of seizure to provide six groups:

(1) Standard: mean arterial pressure above 120 mmHg, no hypoxia or hypoglycæmia, rectal temperature close to 37° C.
(2) Moderate Hypotension: mean arterial pressure at 70–75 mmHg.
(3) Severe Hypotension: mean arterial pressure at 50 mmHg.
(4) Hypoxia: arterial oxygen tension at 50 mmHg.
(5) Hypoglycæmia: non-fed animals, with blood glucose close to 3·0 μmol/g.
(6) Hyperthermia: rectal temperature at 40° C.

Microvacuolation and ischæmic cell change were identified by light microscopy in scattered neurons in the cortex (principally in the outer layers) in animals in three groups (Standard, Severe Hypotension and Hyperthermia). Similar neuronal changes were seen in the hippocampus (predominantly in the h_1 or Sommer sector) in the Standard and Hyperthermia Groups. It is tentatively proposed that neuronal damage in animals with unrestricted cerebral oxygen and glucose availability is due to oxidative mechanisms in cells with excessively enhanced neuronal activity and that lesions caused by failing energy production do not appear until severe degrees of hypoxia are reached.

ACKNOWLEDGEMENTS

The assistance of Kerstin Beirup and Lena Barnekow is gratefully acknowledged. This study was supported by grants from the Swedish Medical Research Council, Förenade Liv Insurance Co., Stockholm, Segerfalkska Stiftelsen and Föreningen Margaretahemmet. B.S.M. is supported by the Wellcome Trust and the Medical Research Council (UK) and received a Travel Grant under the Royal Society European Exchange Scheme.

REFERENCES

BARBER, A. A. and BERNHEIM, F. (1967) Lipid peroxidation: its measurement, occurrence, and significance in animal tissues. *Advances in Gerontological Research*, **2**, 355–403.

BLENNOW, G., FOLBERGROVÁ, J., NILSSON, B. and SIESJÖ, B. K. (1978*a*) Cerebral metabolic and circulatory changes in the rat during sustained seizures induced by dl-homocysteine. *Brain Research, Amsterdam*. In press.

—— —— —— —— (1978*b*) Effects of bicuculline-induced seizures on cerebral metabolism and circulations of rats rendered hypoglycaemic by starvation. *Annals of Neurology*, **4**, 281–283.

BLENNOW, G., NILSSON, B. and SIESJO, B. K. (1977) Sustained epileptic seizures complicated by hypoxia, arterial hypotension, or hyperthermia: effects on cerebral energy state. *Acta Physiologica Scandinavica*, **100**, 126–128.

—— —— —— (1978*c*) Cerebral functional and metabolic changes provoked by hypoxia during bicuculline-induced seizures in rats. *Annals of Neurology*. In press.

BORGSTRÖM, L., CHAPMAN, A. G. and SIESJO, B. K. (1976) Glucose consumption in the cerebral cortex of rat during bicuculline-induced status epilepticus. *Journal of Neurochemistry*, **27**, 971–973.

BRIERLEY, J. B. (1976) Cerebral hypoxia. In: *Greenfield's Neuropathology*. Edited by W Blackwood and J. A. N. Corsellis. London: Arnold, pp. 43–85.

BROWN, A W. and BRIERLEY, J. B. (1968) The nature, distribution and earliest stages of anoxic ischæmic nerve cell damage in the rat brain as defined by the optical microscope. *British Journal of Experimental Pathology*, **49**, 87–106.

—— —— (1973) The earliest alterations in rat neurones after anoxia-ischaemia. *Acta Neuropathologica, Berlin*, **23**, 9–22.

CARLSSON, C., HÅGERDAL, M. and SIESJÖ, B. K. (1976) The effect of hyperthermia upon oxygen consumption and upon organic phosphates, glycolytic metabolites, citric acid cycle intermediates and associated amino acids in rat cerebral cortex. *Journal of Neurochemistry*, **26**, 1001–1006.

CASPERS, H. and SPECKMANN, E.-J. (1972) Cerebral pO_2, pCO_2 and pH: changes during convulsive activity and their significance for spontaneous arrest of seizures. *Epilepsia*, **13**, 699–725.

CHAPMAN, A. G., MELDRUM, B. S. and SIESJÖ, B. K. (1977) Cerebral metabolic changes during prolonged epileptic seizures in rats. *Journal of Neurochemistry*, **28**, 1025–1035.

CORSELLIS, J. A. N. and MELDRUM, B. S. (1976) Epilepsy. In: *Greenfield's Neuropathology*. Edited by W. Blackwood and J. A. N. Corsellis. London: Arnold, pp. 771–795.

DEMOPOULOS, H. B., FLAMM, E. S., SELIGMAN, M., POWER, R., PIATRONITRO, D. and RANSOHOFF, J. (1977) Molecular pathology of lipids and CNS membranes. In: *Oxygen and Physiological Function*. Edited by F. F. Jöbsis. 60th FASEB Annual Meeting, Professional Information Library, Dallas. pp. 491–508.

FRIDOVICH, I. (1974) Superoxide dismutases. *Advances in Enzymology*, **41**, 35–97.

—— (1975) Superoxide dismutases. *Annual Review of Biochemistry*, **44**, 147–159.

GURDJIAN, E. S., WEBSTER, J. E. and STONE, W E. (1947) Cerebral metabolism in metrazol convulsions in the dog. *Research Publications, Association for Nervous and Mental Diseases*, **26**, 184–204.

JÖBSIS, E. E., O'CONNOR, M., VITAK, A. and WREMON, H. (1971) Intracellular redox changes in functioning cerebral cortex. I. Metabolic effects of epileptiform activity. *Journal of Neurophysiology*, **5**, 735–749.

JOHANSSON, B. and NILSSON, B. (1977) The pathophysiology of the blood-brain barrier dysfunction induced by severe hypercapnia and by epileptic brain activity. *Acta Neuropathologica, Berlin*, **38**, 153–159.

MCLARDY, T. (1974) Pathogenesis of epileptic-hypoxic ammonshorn sclerosis: contribution of basal vein constriction by looped posterior cerebral artery. *I.R.C.S., Journal of International Research Communications. Medical Science*, **2**, 1574.

MELDRUM, B. S. and BRIERLEY, J. B. (1973) Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. *Archives of Neurology, Chicago*, **28**, 10–17.

MELDRUM, B. S. and HORTON, R. W. (1973) Physiology of status epilepticus in primates. *Archives of Neurology, Chicago*, **28**, 1-9.

—— and NILSSON, B. (1976) Cerebral blood flow and metabolic rate early and late in prolonged epileptic seizures induced in rats by bicuculline. *Brain*, **99**, 523-542.

—— VIGOUROUX, R. A. and BRIERLEY, J. B. (1973) Systemic factors and epileptic brain damage. Prolonged seizures in paralysed artificially ventilated baboons. *Archives of Neurology, Chicago*, **29**, 82-87.

MOREL, F. and WILDI, E. (1956) Sclérose ammonienne et épilepsies. *Acta Neurologica et Psychiatrica, Belgica*, **56**, 61-74.

MYERS, R. E. (1977) Lactic acid accumulation as cause of brain edema and cerebral necrosis resulting from oxygen deprivation. In: *Advances in Perinatal Neurology*. Edited by R. Korobkin and C. Guilleminault. New York: Spectrum Publishers.

RUDERMAN, N. B., ROSS, P. S., BERGER, M. and GOODMAN, M. N. (1974) Regulation of glucose and ketone-body metabolism in brain of anæsthetized rats. *Biochemical Journal*, **138**, 1-10.

SCHOLZ, W. (1959) The contribution of patho-anatomical research to the problem of epilepsy. *Epilepsia*, **1**, 36-55.

SLATER, T. F. (1972) *Free Radical Mechanisms in Tissue Injury*. London: Pion, pp. 74-90.

SPIELMEYER, W. (1927) Die Pathogenese des epileptischen Krampfes. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **109**, 501-520.

WASTERLAIN, C. G. (1974) Mortality and morbidity from serial seizures: an experimental study. *Epilepsia*, **15**, 155-176.

(*Received May 2, 1978*)

Brain (1978), **101**, 701-715

EFFECT OF ETHANOL ON NEURONAL ACTIVITY IN THE PARIETAL ASSOCIATION CORTEX OF ALERT MONKEYS

by J. HYVÄRINEN, M. LAAKSO, R. ROINE, L. LEINONEN
and H. SIPPEL

(*From the Institute of Physiology, University of Helsinki, and the Research Laboratories of State Alcohol Monopoly (Alko), Helsinki, Finland*)

INTRODUCTION

WORK conducted with electroencephalographic methods has indicated that polysynaptic systems of the brain are more easily depressed by alcohol than the specific sensory receiving areas of the cortex. Thus, in the cat, evoked potentials are depressed in the parietal association cortex and the reticular formation before the somatosensory and auditory cortices are affected (DiPerri, Dravid, Schweigerdt and Himwich, 1968; Perrin, Hockman, Kalant and Livingston, 1974; Kalant, 1975). Typical sensorimotor disturbances produced by alcohol are impairment of eye-hand co-ordination and of simultaneous performance in several tasks (Moskowitz, 1973). The posterior parietal association cortex is involved in eye-hand co-ordination, spatial attention and simultaneous performance of many tasks (Critchley, 1953). Disturbances in these functions were described after World War I by Holmes (1918) for patients who had bilateral gunshot wounds in both posterior parietal association cortices. Moreover, one of the syndromes produced by lesions in the posterior parietal association cortex has been called simultanagnosia because of the incapacity of the patient to attend simultaneously to more than one task (Wolpert, 1924; Luria, Pravdina-Vinarskaya and Yarbuss, 1963).

During recent years microelectrode recording of cellular discharges in the posterior parietal association cortex in awake monkeys has indicated that this region is involved in control of hand and eye movements (Hyvärinen and Poranen, 1974, Mountcastle, Lynch, Georgopoulos, Sakata and Acuna, 1975, Lynch, Mountcastle, Talbot and Yin, 1977, Robinson, Goldberg and Stanton, 1978, Leinonen, Hyvärinen, Nyman and Linnankoski, 1978). It therefore seemed likely that the posterior parietal association cortex might be involved in the neural mediation of the effects of alcohol on sensorimotor co-ordination. We have studied the effects of alcohol on the cellular activity in this region of the monkey (fig. 1), and found that alcohol at many recording sites within this region has an effect on the cellular activity that closely parallels its effect on sensorimotor behaviour.

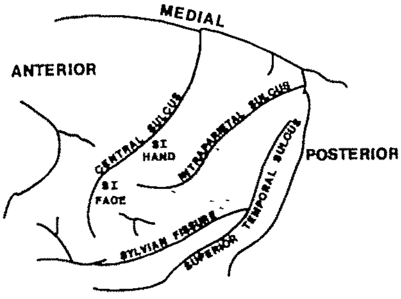


FIG. 1. Diagram of the recording area (stippled) in the lateral part of Brodmann's area 7.

MATERIAL AND METHODS

The effect of alcohol on the cellular activity in the posterior parietal association cortex was studied in seven hemispheres of five non-anæsthetized stump-tailed monkeys (*Macaca speciosa*). Recording of the neuronal activity was done using coarse metal microelectrodes with exposed tips of about 100 μm. These were made of tungsten and covered with glass by a modification of the method described by Levick (1972). They were introduced into the brain with a hydraulic micromanipulator using a modification of the Evarts' technique for recording from non-anæsthetized animals (Evarts, 1968) as described earlier (Hyvärinen and Poranen, 1974). In the experiments the recovery from drug action took several hours, and it was not possible to hold single units in non-anæsthetized, moving animals all this time; therefore multiple unit studies were preferred.

The recording was done in Brodmann's area 7 (fig. 1), which appears to be organized in columns as in other cortical regions (Hyvärinen and Poranen, 1974, Mountcastle *et al.*, 1975). Therefore most neurons recorded simultaneously with a coarse microelectrode respond to similar stimuli, and multiple unit recording indicates adequately the function of the neurons at the site of recording. The multineuronal impulse-activity was filtered with a high-pass filter at 300, 500 or 1000 Hz to eliminate slow waves from the responses. High-pass filtering of the recording completely eliminated the slow waves from the signal leaving only action potential spikes (fig. 2) which were monitored with an oscilloscope and an audiomonitor. Fig. 2 shows multineuronal impulse-activity as recorded before integration. Occasionally an unfiltered slow-wave record (which may be described as a focal intracortical electrocorticogram) was also made. After filtering, the multineuronal impulse-activity was rectified and integrated with the apparatus described by Weber and Buchwald (1965). The time constants were adjusted for optimal responses to peripheral stimuli in the control phase of the experiment and were not changed during the action of alcohol and recovery. A charge time constant of 100 ms and a decay time constant of 225 ms were most commonly used. Because the absolute levels of the responses were not comparable at different recording sites, the amplitudes of the responses were expressed as a percentage of control records. Fig. 2 illustrates the relationship between the raw multiple unit data and the integrated record, and the measurement of the amplitude of the integrated responses. Fig. 10 shows examples of both integrated multineuronal impulse-activity and focal intracortical electrocorticograms.

Thirty-two experiments were made using ethanol in area 7 and two in the primary somatosensory cortex. Recordings were performed in 7 hemispheres of 5 monkeys. The recording site in the lateral part of area 7 (fig. 1) was determined stereotaxically, and in 3 monkeys (5 hemispheres) it was anatomically

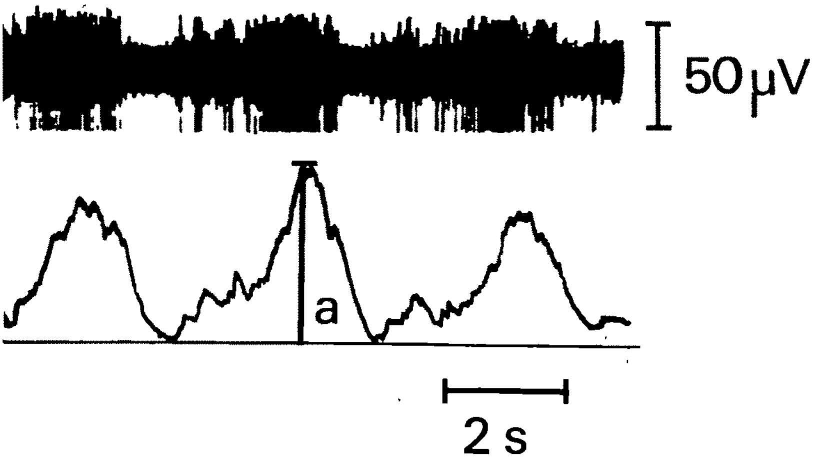


FIG. 2. Raw recording of multineuronal impulse-activity (*upper trace*) and a rectified and integrated record of the same activity (*lower trace*). The figure shows three control responses to reaching for a food reward with the arm ipsilateral to the recording site The amplitude calibration (50 μV) applies only to the raw recording. The measurement of the amplitude (a) of the integrated waves from the baseline of recording is indicated for the middle response. The average (±SD) values calculated from recordings made during the action of alcohol were expressed as a percentage of the average control values.

verified after the animals were killed. In 2 monkeys (2 hemispheres) the same stereotaxic co-ordinates were used and functional criteria also indicated the same region of recording. These 2 monkeys are alive at the time of writing and the recording site has not been anatomically confirmed.

In initial experiments alcohol was given by mouth, and it was observed that the absorption, elimination and toxicity of ethanol in this species are comparable to those in man (Hyvärinen, Sippel, Linnankoski, Roine, Virtanen, Olkinuora and Nieminen, 1976). Since the blood alcohol levels rose slowly after peroral administration we decided to give alcohol intravenously through a catheter permanently implanted through the jugular vein (Craig, Trost and Talley, 1969). Under general anæsthesia a catheter was introduced into the right atrium of the heart as indicated by pulsations of the blood column, fixed in place and its opposite end passed under the skin to the recording cylinder, capped and fixed on the outer side of the recording cylinder with a piece of perspex. The catheter was rinsed with sterile heparinized saline solution and penicillin was given through it daily. With these precautions the catheters remained patent for three to five weeks without infectious complications. Alcohol was infused rather rapidly as 25 per cent (v/v) solution in physiological saline giving 0·5 g/kg in approximately five minutes. Several infusions were given until the effect was clear or toxic symptoms started, which usually occurred after a dosage of 2 to 3 g/kg. After each infusion the catheter was washed with saline including a small amount of heparin. In 11 experiments the same catheter was used to obtain samples of central blood for estimation of blood ethanol concentrations. For this purpose blood samples of 0·1 ml were immediately pipetted into 1·8 ml of ice cold 0·6 M perchloric acid, containing 10 mM thiourea, and shaken, the suspensions were then centrifuged at 4000 × g for fifteen minutes at 4° C. Ethanol concentrations in the protein-free supernatants were estimated by head-space gas chromatography (Eriksson, 1973).

The behavioural action of alcohol was monitored by observing the monkey's reaching for food rewards. Raisins or pieces of banana were moved close to the monkey in the experimenter's hand or on a stick, and the monkey's reaching accuracy and speed was scored by the experimenter. Ten points were given for rapid and accurate grasping of the food and 0 points for no attempt to reach. Intermediate values were given for intermediate accuracies and speeds. Three observers did the scoring, getting results which did not differ from each other by more than ±10 per cent. In some experiments the latency of reaching for food reward was separately measured using a specially constructed food well with electric timing. The inverse of the latency correlated well with the reaching accuracy scores. Eye movements were observed by recording electro-oculograms with four Ag-AgCl electrodes chronically implanted around the orbits (Bond and Ho, 1970).

RESULTS

Effects on Spontaneous Activity

Alcohol produced a rhythmic spontaneous discharge of impulses at most recording sites. An example of this rhythm is shown in fig. 3. The prevalence of the rhythm was determined by measuring the time that the discharge was rhythmic and expressed as a percentage of the total recording time as indicated in fig. 3.

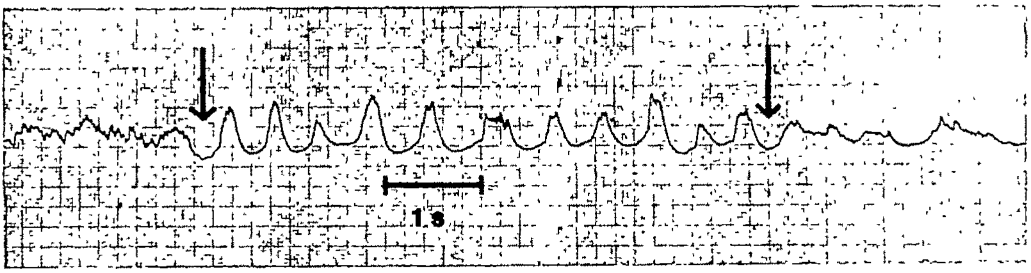


FIG. 3. A rhythmic period in the record of integrated multineuronal impulse-activity For measurement of the percentage of time of rhythmic discharge 40 s of spontaneous activity was recorded, and the rhythmic periods in it were marked as indicated in the figure. Periods containing three or more well discernible successive waves were considered as rhythmic activity. The duration of these periods was measured and expressed as a percentage of the total duration of the recording.

The dominant frequency of the rhythm was determined by counting the number of distinct waves per unit time during the rhythmic periods. With an increasing dosage of alcohol the prevalence of the rhythm increased and its frequency decreased. Some rhythmic discharge appeared after 0·5 to 1 g/kg of alcohol and with low dosage it was more common when the monkey's eyes were shut or covered (fig. 4). With an increasing dose the rhythm gradually became more prevalent until the spontaneous activity was continuously rhythmic. The proportion of rhythmic activity correlated inversely with the monkey's reaching accuracy (fig. 4).

The dominant frequency of the rhythm recorded in the multiple unit discharge ranged from 3·5 to 1 Hz corresponding to the delta region of EEG frequencies. There was an inverse relationship between the dose of ethanol (or blood ethanol level) and the frequency of the spontaneous rhythm, but the frequency of the rhythm was not affected by closing of the eyes as was its occurrence (fig. 5).

Effects on Cellular Responses to Reaching and Other Motor Activity

Twelve of the 32 recording sites in area 7 were related to voluntary motor activity of the hand. At these sites alcohol was more commonly effective than at

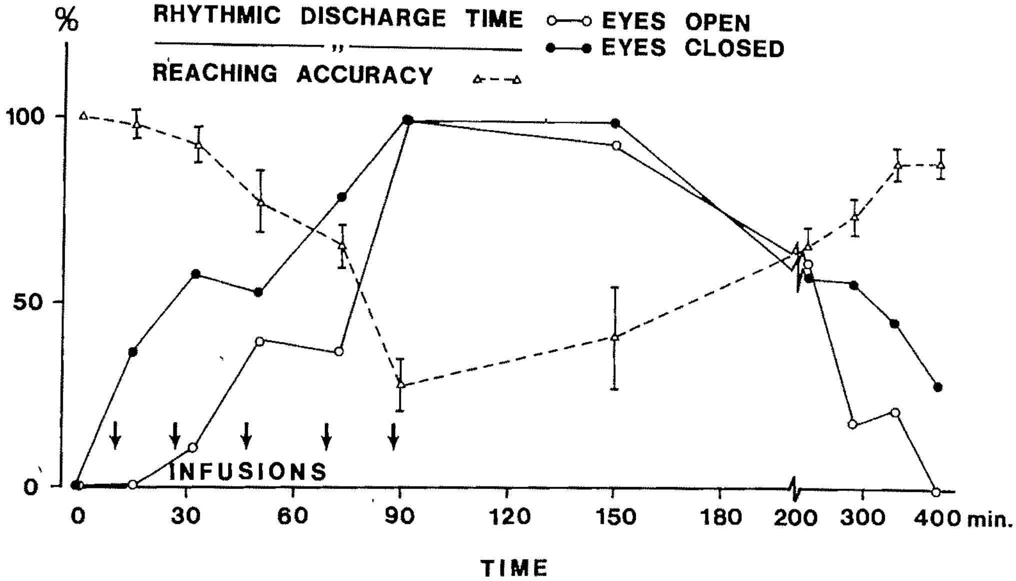


FIG. 4. The percentage of rhythmic discharge time in spontaneous multineuronal impulse-activity during infusion of alcohol and recovery from its action at a recording site in area 7 Five infusions of 0·5 g/kg body weight of alcohol were given intracardially (arrows). The dotted line indicates the percentage score of the monkey's reaching accuracy A peak blood alcohol level of 400 mg/100 ml was reached at 100 min from the start of the experiment

the sites activated by sensory stimuli (Table 1). Ten of these sites were active during reaching movements made by the monkey, that is, the activity increased when the monkey was actively reaching for food rewards (Hyvärinen and Poranen, 1974, Mountcastle *et al.*, 1975). The activity at two recording sites correlated with manual grasping of the target. Fig. 6 shows an example of the effect of alcohol on the responses to reaching with the contralateral hand. At this recording site the cellular activity started when food was brought within the reach of the monkey and he started arm movements toward the food. The activity ceased when the monkey had the food firmly in his hand. The reaching movements became

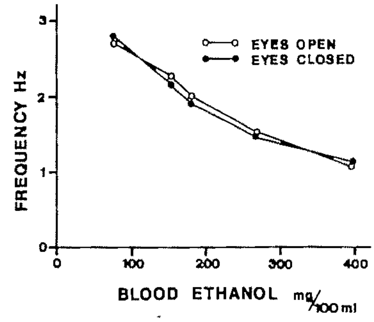


FIG 5. The dominant frequency of the spontaneous multineuronal impulse-rhythm as a function of blood ethanol level in another experiment The dominant frequency was approximately 3 Hz when the blood ethanol was 100 mg/100 ml and 1 Hz when the blood ethanol was 400 mg/100 ml. The frequency was not affected by closing the eyes

characteristically slower and clumsier with the increasing dose of alcohol and simultaneously the cellular discharge also diminished.

Under the influence of alcohol a close correlation between the amplitude of integrated multiple unit responses and the monkey's reaching accuracy was observed in 8 of the 12 locations that responded to reaching or grasping (Table 1). At the remaining 4 recording sites the responses were not affected by alcohol although the monkey performed very poorly in reaching for the reward. We found no features in the control responses that would indicate whether a particular site was sensitive to alcohol or not.

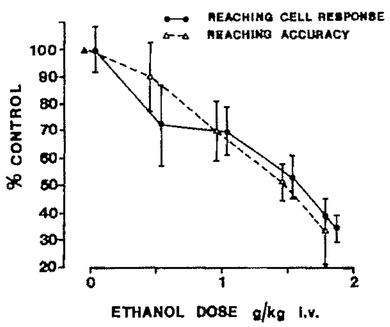


FIG. 6. Results of an experiment performed at a site responsive to reaching movements performed with the contralateral hand. When the monkey was reaching for a food reward the neuronal responses and the monkey's reaching accuracy were simultaneously recorded. Both fell uniformly with increasing ethanol dose. Means and standard deviations of 10 responses expressed as a percentage of the mean values of control record.

TABLE 1. EFFECT OF ALCOHOL ON MULTI-NEURONAL RESPONSES AT DIFFERENT RECORDING SITES IN AREA 7

Type of activity	*Effect*		*No effect*		*Total*	
	N	%	*N*	%	*N*	%
1. Motor (reaching, grasping)	8	67	4	33	12	38
2. Visual (complex visual phenomena)	5	50	5	50	10	31
3. Somatosensory (skin, muscle)	3	30	7	70	10	31
Total	16	50	16	50	32	100

Effects on Visual Responses

Ten of the recording sites were activated by visual stimuli. All these sites responded to complex visual stimuli of the type described by Hyvärinen and Poranen (1974) and Leinonen *et al.* (1978). The activity at these sites was triggered by one of the following types of visual stimuli: a new object not seen by the monkey before, visual approach toward the monkey, rotatory movement of three-dimensional objects, or movement of large objects in the monkey's visual field. The responses were not dependent on eye movements except at one locus where both eye movements and moving visual stimuli triggered activity. Visual fixation in itself was not enough to trigger responses at these sites as fixation of food did not result in a response.

Fig. 7 shows the effect of alcohol on a complex visual response. At this site cellular activity was triggered by new objects that were brought into the monkey's visual field. As such objects we used various laboratory tools, ten of which were consecutively presented to the monkey to obtain the mean and standard deviation values shown in the figure. Fixation of food did not activate this site nor did repeated presentations of the same object. As can be seen in the figure the responses diminished with increasing blood alcohol concentration and recovered during elimination of alcohol. The amplitudes of the responses also correlated with the reaching accuracy of the monkey. A difference between the effects of rising and falling alcohol concentrations was observed in this experiment as well as in a few others. In fig. 7 a blood concentration of 200 mg/100 ml during the rising phase of intoxication reduced the cellular responses and reaching accuracy nearly by half, whereas, during the recovery phase, almost normal cellular and behavioural responses were observed at this level of blood alcohol, indicating an acute tolerance effect.

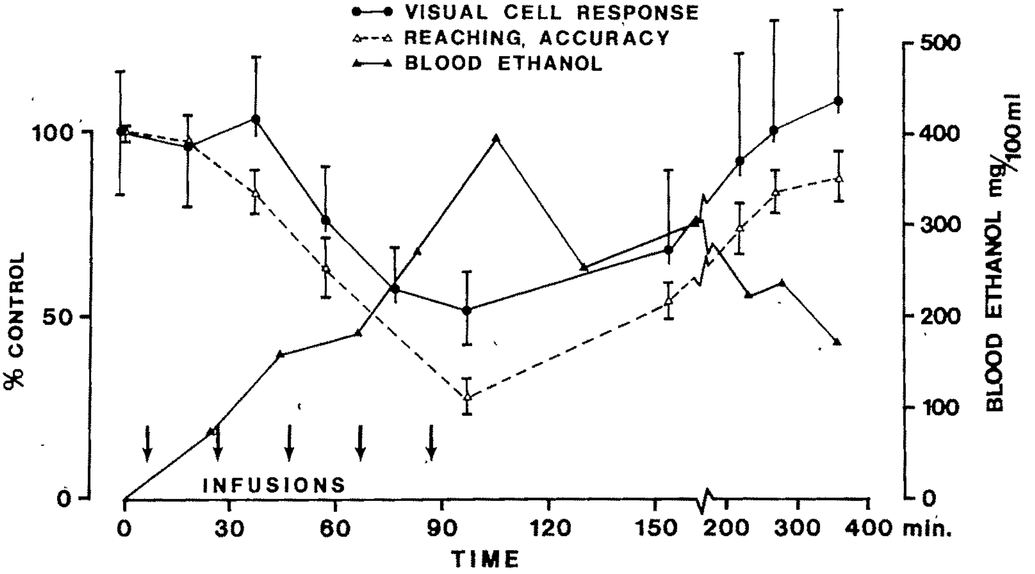


FIG. 7 Results of an experiment performed at a site responsive to introduction of new objects into the monkey's field of vision. The arrows indicate intracardiac infusions of 0·5 g/kg of alcohol each giving a total of 2·5 g/kg. The integrated multineuronal impulse-responses and the monkey's reaching accuracy (mean ±SD of 10 responses) are expressed as a percentage of mean control values Ten different laboratory tools and other objects not previously seen by the monkey and conveniently available were successively presented in each phase of the experiment. Repeated presentations of the same stimulus object, even food that triggered visual fixation, did not activate these cells

At 5 of the 10 visual recording sites alcohol significantly reduced the responses, whereas at the other 5 sites with this type of response no effect of alcohol on the responses was observed. At the latter recording sites the cellular responses remained unchanged even when the monkey was heavily intoxicated and did not seem to attend to the stimuli. Neither could we predict on the basis of the control recording whether the responses of the visual recording sites would be influenced by alcohol or not.

Effects on Somatosensory Responses

Ten of our recording sites were activated by somatosensory stimuli. Seven of these sites were related to cutaneous stimulation, and three that were unresponsive to cutaneous stimulation responded to squeezing of the underlying muscles. Such responses were not elicited as readily as in the adjacent primary somatosensory area, where repeated passive stimulation always evokes a stereotyped response (Hyvärinen and Poranen, 1978). In area 7 the responses habituate quickly on repeated stimulation and they are usually best elicited with relatively large stimuli (Hyvärinen and Poranen, 1974; Leinonen *et al.*, 1978).

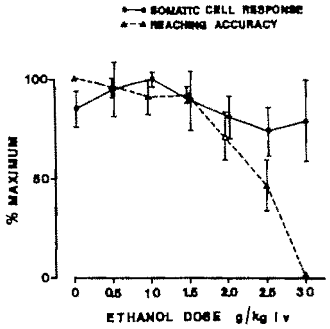


FIG. 8. Results of an experiment performed in area 7 at a site responsive to cutaneous touch stimuli on the contralateral palm and fingers. Although the reaching accuracy of the monkey fell as a function of the ethanol dose no significant change occurred in the amplitude of the integrated cutaneous multineuronal responses. Mean ±SD of 10 responses.

The somatosensory recording sites were on the average more resistant to the action of alcohol than the other types of recording sites. A decrease of the responses was observed at only 3 of the 10 sites whereas responses at 7 sites remained uninfluenced by moderate concentrations of alcohol. Fig. 8 indicates the stability of the responses at a site responsive to touch stimuli on the hand. Up to 3 g/kg of alcohol was given to the monkey resulting in a complete cessation of the animal's reaching behaviour. The cutaneous responses were not, however, appreciably reduced.

Fig. 9 shows results of an exceptional experiment where both cutaneous and visual responses could be recorded simultaneously. A response was obtained from an approaching visual stimulus but a smaller response was also evoked by a cutaneous touch stimulus when the monkey's eyes were covered. The best response was evoked by cutaneous touch when the monkey could see the touching. These three responses were differentially sensitive to the action of alcohol. The purely cutaneous responses (obtained with eyes covered) were least influenced and the responses to approaching visual stimuli were most influenced.

We made a few experiments with an exceptionally large alcohol dosage to see whether this would abolish responses to somatosensory stimulation in area 7, and also to observe the fate of the responses in the adjacent primary somatosensory cortex. In three experiments 5 to 7 g/kg of ethanol was given by mouth during several hours. These dosages were large enough to produce a comatose state in the monkeys (Hyvärinen *et al.*, 1976). During the comatose phase the somatosensory responses disappeared at two of these recording sites in area 7 but remained uninfluenced at one site. Fig. 10 shows spontaneous activity and responses at a site in area 7 responsive to cutaneous touch on the hand. The upper curve in each pair is the integrated multiple unit activity and the lower one the unfiltered focal electrocorticogram. The responses did not decrease until 7 g/kg of alcohol had been given; then the monkey suddenly became nonreactive to its environment. At the same time the responses to cutaneous stimulation also disappeared and only periodic spontaneous bursts of activity remained. We then quickly shifted the electrode to the adjacent primary somatosensory cortex where we still obtained

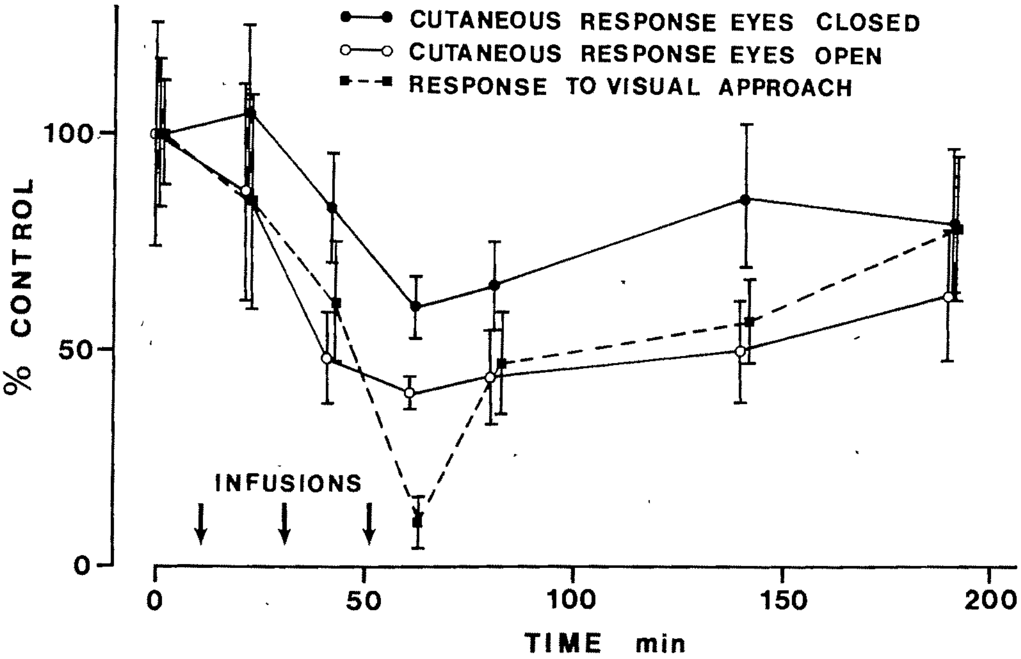


FIG. 9. Results of an experiment performed at a site responsive to visual stimuli approaching the monkey's face and to cutaneous stimulation of the contralateral cheek. All responses are expressed as a percentage of the corresponding value in the control record. The ethanol infusions (arrows) were 1, 1 and 0·8 g/kg The response to visual approach was the most sensitive to alcohol and the cutaneous response obtained with eyes covered was the least sensitive. Mean ±SD of 10 responses

strong responses to touching of the hand (fig. 10D). In another experiment in which the recording was continuously done in the primary somatosensory cortex no effect of alcohol was observed.

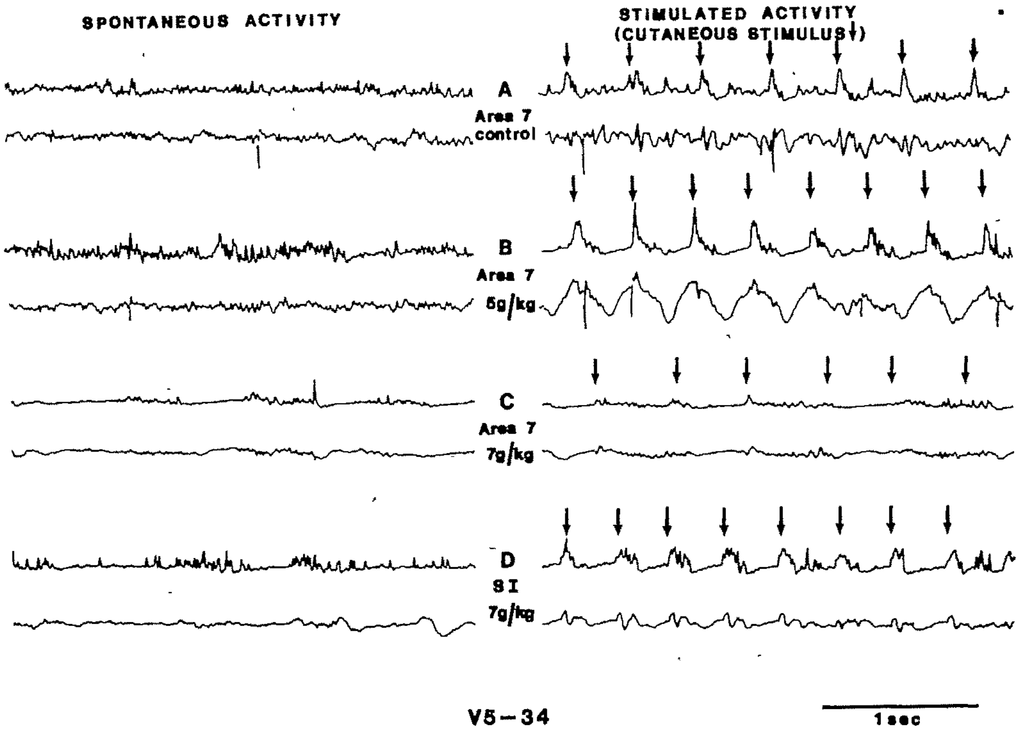


FIG. 10. Integrated multineuronal impulse activity and focal intracortical electrocorticogram at a recording site in area 7 responsive to cutaneous stimulation of distal parts of all limbs. The left side of the picture shows spontaneous activity and the right side the responses to cutaneous stimuli delivered on the contralateral hand, the site that gave the best responses. Both integrated multineuronal impulse-activity and focal intracortical electrocorticograms are shown. In each pair the top record is the integrated multineuronal impulse-activity and the lower record the corticogram obtained through the same electrode without filtering. A, control recording. B, after peroral administration of 5 g/kg of alcohol. C, after additional 2 g/kg of alcohol D, the electrode was shifted to the adjacent primary somatosensory cortex (SI) immediately after record C Here the tissue was still strongly reactive to cutaneous stimulation of the contralateral hand although the monkey did not react to any stimulation and no responses were recorded in area 7.

DISCUSSION

The multiple unit recording method used in this study is intermediate between recording of single units and focal intracortical electrocorticograms. Use of intracortical microelectrodes with a relatively large uninsulated area at the tip (~100μm) allows monitoring of the activity of a group of cortical cells consisting of approximately 5 to 10 neurons. However, without filtering, the record includes the focal slow waves which, because of their magnitude, tend to dominate the recording. High-pass filtering at 100 Hz or higher eliminates the slow waves, leaving only the multi-unit discharge composed of the action potentials of cortical neurons (Buchwald and Grover, 1970). Rectification and integration of this activity gives a record whose amplitude reflects the quantity of action potential firing in the group of cells recorded (fig. 2). In this work the multineuronal impulse-activity was filtered at 300 Hz or higher before integration; we could not detect any slow-wave activity in these records. Although we did not record from single cortical neurons it can be inferred, on the basis of the multiple unit studies, that most of the cells at the site of recording respond to stimuli and react to drugs in the way indicated by the integrated multineuronal impulse-activity. The unfiltered, intracortically-recorded focal electrocorticogram also reflects the activity of the elements in a small volume of cortical tissue (fig. 10), but because of the slow-waves present in such records their interpretation is more complex than that of the filtered recordings composed of only action potential activity. However, the diversity of the response types encountered with focal recording suggests that EEG recordings performed from the cortical surface or from the scalp average activity from quite different types of functional cell groups. Because of this averaging the surface EEG appears as a quite indiscriminate indicator of cortical function.

One of the characteristic actions of alcohol is its deteriorating effect on the accuracy of control of movement, particularly of eye-hand co-ordination. The ability to perform several tasks simultaneously is reduced under the influence of alcohol (Moskowitz, 1973). Patients who have posterior parietal lesions demonstrate defects that resemble these effects of alcohol. Thus bilateral lesions of this part of the cortex produce disturbances in eye movements and directed movements of the hand (Holmes, 1918; Critchley, 1953), and occasionally lesions produce an inability to attend visually to more than one target at a time (Balint, 1909; Wolpert, 1924; Luria *et al.*, 1963). In the corresponding part of the cortex in the monkey the activity of neurons is related to eye and hand movements and to complex sensory stimuli (Hyvärinen and Poranen, 1974; Mountcastle *et al.*, 1975; Lynch *et al.*, 1977; Yin and Mountcastle, 1977; Robinson *et al.*, 1978; Leinonen *et al.*, 1978). It therefore seemed possible that effects of alcohol in this area would reflect the effect it has on sensorimotor performance. In this study such effects were seen at one half of the recording sites in the posterior parietal association area 7, whereas with the dose (up to 2 or 3 g/kg) commonly used, the other half of the recording sites remained uninfluenced. The effects were most common at the recording sites where the activity was related to motor behaviour of the monkey, less common at recording sites characterized by responses to complex visual stimuli and least common at the recording sites with somatosensory responses. With a larger dose of alcohol, however, more of the somatosensory sites were affected whereas no influence of alcohol was observed in the primary somatosensory cortex.

It is obvious that the posterior parietal association cortex is functionally not homogeneous but that various groups of cells (columns) respond to different types of stimuli (Hyvärinen and Poranen, 1974; Mountcastle *et al.*, 1975). However, this work shows that in addition to this complexity of functional connections the sensitivity to drugs is also unevenly distributed in this region. It was not possible to predict on the basis of the type of the control response whether it would be influenced by alcohol or not. The fact that an increase of the dose brought additional somatosensory recording sites under the influence of alcohol suggests that the uneven distribution of effects may be a question of dose. With a dose that was sufficient to disturb sensorimotor co-ordination severely only half of the recording sites were affected, but with a dose that produces a comatose stage most (but not all) sites in area 7 become apparently unresponsive. This area is far more sensitive to alcohol than the adjacent primary somatosensory cortex. It is well known that general anæsthesia does not block the responses in the primary somatosensory cortex whereas it does so in the association areas (Albe-Fessard and Fessard, 1963; Thompson, Johnson and Hoopes, 1963).

It has previously been reported that alcohol slows the rhythms of the EEG as do other depressant drugs (Hogans, Moreno and Brodie, 1961; Sauerland and Harper, 1970). This effect was very clearly reflected in the multineuronal impulse-activity recorded in this study. A close-to-linear relationship between the frequency of the dominant rhythm of the multiple unit discharge and the blood alcohol level (fig. 5) was observed. The appearance of a spontaneous slow rhythm is probably an indication of partial functional decoupling of the recording site from other brain mechanisms. The occurrence of rhythmic multiple unit discharge also correlated with the impairment of the monkey's sensorimotor co-ordination (fig. 4). The fact that closing the eyes increased the occurrence of the rhythm at moderate alcohol doses indicates the generalized influence of vision on the spontaneous activity in this part of the cortex.

It has been suggested that the effect of alcohol depends on the complexity of synaptic contacts to the site of recording (Wallgren and Barry, 1970; Himwich and Callison, 1972; Kalant, 1975). On the basis of EEG and evoked potential studies the cortical association zones and the reticular formation of the brain-stem, a polysynaptic structure, were reported to be quite sensitive (DiPerri *et al.*, 1968; Perrin *et al.*, 1974). Our findings in the parietal association area 7 support this interpretation, since no effects were observed in the primary somatosensory cortex, and within area 7 the effect correlated with complexity of response properties. The somatosensory afferents arriving in area 7 from the adjacent somatosensory cortex and from area 5 (Jones and Powell, 1970) form more direct connection with the cells in area 7 than the visual afferents, which must arrive through a more complex route (Kaas, Lin and Wagor, 1977, Yin and Mountcastle, 1977). The more complex route could explain the greater sensitivity of the visual responses to alcohol. However, these results indicate that two cortical loci that appear functionally similar may have different synaptic contacts from the pharmacological points of view.

SUMMARY

The effect of alcohol was studied in alert monkeys on the cellular mechanisms of the posterior parietal association cortex, a region that normally participates in visuo-spatial co-ordination of hand movements. In thirty-two experiments, the effects of intracardiac administration of ethanol were monitored by the intracortical multiple-unit recording technique. Alcohol produced rhythmic groupings of the spontaneous impulse activity; the rhythm was accentuated by closing the eyes. The dominant frequency of this rhythm (3·5 to 1 Hz) correlated inversely with the blood alcohol level. Three groups of response types were studied in Brodmann's area 7. At 8 of 12 recording sites, a close correlation was observed between the monkey's reaching accuracy and the magnitude of integrated multineuronal responses to reaching with the contralateral arm under visual guidance, or to grasping an object. Half of the 10 recording sites which were activated by complex visual stimulation also showed a close correlation with the behavioural action of alcohol. Least sensitive to alcohol were somatosensory responses; only 3 of 10 of such recording sites were influenced by moderate doses of alcohol. Larger doses producing coma increased the proportion of responses blocked by alcohol, whereas no effects were observed in the adjacent primary somatosensory cortex.

Our results show that the posterior parietal association cortex is very sensitive to the action of alcohol. Moreover, these findings support the theory that the action of alcohol in various parts of the central nervous system depends on the complexity of synaptic contacts to the location under study.

ACKNOWLEDGEMENTS

This work has been supported by a grant from the Finnish Foundation for Alcohol Studies. We wish to thank Mr. Ilkka Linnankoski, Mrs. Katriina Laurén, Mrs. Ritva Kettunen and Mrs. Pirkko Johansson for able technical assistance and Professor Henrik Wallgren for encouragement and comments.

REFERENCES

ALBE-FESSARD, D. and FESSARD, A. (1963) Thalamic integrations and their consequences at the telencephalic level. *Progress in Brain Research*, **1**, 115–148.

BALINT, R. (1909) Sehlenlähmung des 'Schauens', optische Ataxie, raümliche Störung der Aufmerksamkeit. *Monatsschrift fur Psychiatrie und Neurologie*, **25**, 51–81.

BOND, H. W. and HO, P. (1970) Solid miniature silver-silver chloride electrodes for chronic implantation. *Electroencephalography and Clinical Neurophysiology*, **28**, 206–208.

BUCHWALD, J. S. and GROVER, F. S. (1970) Amplitudes of background fast activity characteristic of specific brain sites. *Journal of Neurophysiology*, **33**, 148–159.

CRAIG, D. J., TROST, J. G. and TALLEY, W. (1969) A surgical procedure for implantation of a chronic indwelling jugular catheter in the monkey. *Laboratory Animal Care*, **19**, 237–239

CRITCHLEY, M. (1953) *The Parietal Lobe*. London: Edward Arnold.

DIPERRI, R., DRAVID, A., SCHWEIGERDT, A. and HIMWICH, H. E. (1968) Effects of alcohol on evoked potentials of various parts of the central nervous system of cat. *Quarterly Journal of Studies on Alcohol*, **29**, 20–37.

ERIKSSON, J. P. C. (1973) Ethanol and acetaldehyde metabolism in rat strains genetically selected for their ethanol preference. *Biochemical Pharmacology*, **22**, 2283–2292.

EVARTS, E. V. (1968) A technique for recording activity of subcortical neurons in moving animals. *Electroencephalography and Clinical Neurophysiology*, **24**, 83–86.

HIMWICH, H. E. and CALLISON, D. A. (1972) The effects of alcohol on evoked potentials of various parts of the central nervous system of the cat. In: *The Biology of Alcoholism.* Edited by B. Kissin and H. Begleiter. New York· Plenum Press, *Vol. 2*, pp. 67–84.

HOGANS, A. F., MORENO, O. M. and BRODIE, D. A. (1961) Effects of ethyl alcohol on EEG and avoidance behaviour of chronic electrode monkeys. *American Journal of Physiology*, **201**, 434–436.

HOLMES, G. (1918) Disturbances of visual orientation. *British Journal of Ophthalmology*, **2**, 449–468, 506–516.

HYVÄRINEN, J. and PORANEN, A. (1974) Function of the parietal associative area 7 as revealed from cellular discharges in alert monkeys. *Brain*, **97**, 673–692.

—— —— (1978) Receptive field integration and submodality convergence in the hand area of the postcentral gyrus of the alert monkey. *Journal of Physiology, London.* In press.

—— SIPPEL, H., LINNANKOSKI, I., ROINE, R., VIRTANEN, M., OLKINUORA, J. and NIEMINEN, U. (1976) Absorption and elimination of alcohol in the monkey (*Macaca speciosa*). *Blutalkohol*, **13**, 319–326.

JONES, E. G. and POWELL, T. P. S. (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, **93**, 793–820.

KAAS, J. H, LIN, C. S and WAGOR, E. (1977) Cortical projections of posterior parietal cortex in owl monkeys. *Journal of Comparative Neurology*, **171**, 387–408.

KALANT, H. (1975) Direct effects of ethanol on the nervous system. *Federation Proceedings*, **34**, 1930–1941.

LEINONEN, L., HYVARINEN, J., NYMAN, G. and LINNANKOSKI, I. (1978) Functional properties of neurons in lateral part of associative area 7 in awake monkey. *Experimental Brain Research.* In Press.

LEVICK, W. R. (1972) Another tungsten microelectrode. *Medical and Biological Engineering*, **10**, 510–515.

LURIA, A. R., PRAVDINA-VINARSKAYA, E. N. and YARBUSS, A. L. (1963) Disorders of ocular movement in a case of simultanagnosia. *Brain*, **86**, 219–228.

LYNCH, J. C., MOUNTCASTLE, V. B., TALBOT, W. H. and YIN, T. C. T. (1977) Parietal lobe mechanisms for directed visual attention. *Journal of Neurophysiology*, **40**, 362–389.

MOSKOWITZ, H. (1973) Proceedings: Psychological tests and drugs. *Pharmakopsychiatrie Neuro-psychopharmakologie*, **6**, 114–126.

MOUNTCASTLE, V. B., LYNCH, J. C., GEORGOPOULOS, A., SAKATA, H. and ACUNA, C. (1975) Posterior parietal association cortex of the monkey: Command functions for operations within extra-personal space. *Journal of Neurophysiology*, **38**, 871–908.

PERRIN, R. G., HOCKMAN, C. H., KALANT, H. and LIVINGSTON, K. E. (1974) Acute effects of ethanol on spontaneous and auditory evoked electrical activity in cat brain. *Electroencephalography and Clinical Neurophysiology*, **36**, 19–31.

ROBINSON, D. L., GOLDBERG, M. E. and STANTON, G. B. (1978) Parietal association cortex in the primate: Sensory mechanisms and behavioral modulations. *Journal of Neurophysiology*, **41**, 910–932.

SAUERLAND, E. K. and HARPER, R. M. (1970) Effects of ethanol on EEG spectra of the intact brain and isolated forebrain. *Experimental Neurology*, **27**, 490–496.

THOMPSON, R. F., JOHNSON, R. H. and HOOPES, J. J. (1963) Organization of auditory, somatic sensory and visual projection to association fields of cerebral cortex in cat. *Journal of Neurophysiology*, **26**, 343–364.

WALLGREN, H. and BARRY, H. (1970) *Actions of Alcohol.* Amsterdam: Elsevier. 2 vols.

WEBER, D. S. and BUCHWALD, J. S. (1965) A technique for recording and integrating multiple unit activity simultaneously with the EEG in chronic animals. *Electroencephalography and Clinical Neurophysiology*, **19**, 190–192.

WOLPERT, I. (1924) Die Simultanagnosie—Störung der Gesamtauffassung. *Zeitschrift fur die gesamte Neurologie und Psychiatrie*, **93**, 397–415.

YIN, T. C. T. and MOUNTCASTLE, V. B. (1977) Visual input to the visuomotor mechanisms of the monkey's parietal lobe. *Science*, **197**, 1381–1383.

(*Received May 4, 1978*)

Brain (1978), **101**, 717–719

NOTICES OF RECENT PUBLICATIONS

Scientific Approaches to Clinical Neurology. Vols. I and II. Edited by E. S. Goldensohn and S. H. Appel. 1977. Pp. 2040. London: Henry Kimpton. Philadelphia: Lea and Febiger. Price £150.00.

In their preface the editors write that the concept of this work must be ascribed to Dr. Milton Shy, who had begun to assemble authors before his lamented premature death in 1967. Dr. Shy's idea was 'to incorporate scientific knowledge relevant to neurological diseases into a clinical textbook of neurology'. Consequently the emphasis has been on advances in basic science which have contributed to our understanding of neurological disease. No attempt has been made to record all our knowledge of clinical neurology. The distinguished contributors are largely American, but there are representatives from other countries, including Bannister, Guttmann, Hopkins and Walton from Britain.

Internal evidence, that is the references and the authors' preface, indicates that completion has been a lengthy process. Thus the references in some chapters are limited to the 1960s, although addenda are included which bring the story more up to date. The reviewer does not envy the editors their task of assembling so much material from so many authors and the subsequent preparation of the scripts for publication. It is sad that the apparent delay in publication has meant that this large work does not include accounts of important recent additions to knowledge. Admittedly there are some chapters which contain as much contemporary information as the reader can properly expect. What is the answer to problems of time which confront the editors of compendia and their contributors? There are conspicuous examples of much smaller yet comprehensive neurological works which appear in regular new editions and contrive to be up to date. While the solution is probably quite impracticable and financially impossible, one would look forward to an early second edition of this remarkable enterprise. Alternatively, the reader must turn to publications which are more limited in scope, the well prepared monograph or the multi-author contribution on a single theme.

The two volumes are handsomely produced and carefully edited. The contributors write with authority and their names are sufficient guarantee of the quality of Scientific Approaches. Together the books weigh some five kilogrammes and can only be read comfortably at desk or table. At £150 this work is unlikely to find a place in many British departmental libraries.

R. A. HENSON

Pathogenesis of Human Muscular Dystrophies. Edited by L. P. Rowland. 1977. Pp. 895. Amsterdam: Exerpta Medica. Price Dfl. 164.00.

This large (895 pages) and expensive (£34.00) book is the Proceedings of the Fifth International Scientific Conference of the Muscular Dystrophy Association Inc. of the United States, which took place in June 1976.

It is a valuable collection of 70 papers on many aspects of neural and muscular structure and function, including short reviews by elder statesmen on philosophy of muscle research, neural control of muscle and electrophysiology. A large section is devoted to the neuromuscular junction, commencing with a beautiful account, with persuasive illustrations, of the advantages of ultrafast freezing combined with low temperature fixation (J. E. Heuser) in preserving fine structure. This section also contains several contributions to the growing body of acetyl choline receptor research with papers almost exclusively concerned with human myasthenia and experimental allergic myasthenia gravis. These contributions are full of technical points and references which will be of interest to many.

The neurogenic theories are explored by several authors concerned almost entirely with electromyography. A. J. McComas revises the 'sick motor neurone' concept in relation to the several dystrophies, indicating the 'uncertain' position of Duchenne dystrophy and the likelihood that patients with myotonic dystrophy and the Fukuyama dystrophies, together with proximal muscle atrophy of late-onset, may have abnormalities of motor neurons. The discussion of the 'neurogenic' papers evokes, from noted authorities, important, highly technical and critical comments about many of the papers.

The most important section for the students of dystrophies *per se* seeks 'clues from physiology, morphology and biochemistry' to track down the 'site of the lesion'. Physiological papers discuss contractile mechanisms and membrane excitability with evidence presented for reduced excitability in Duchenne dystrophy, contractility defects and abnormal chemosensitivity. A question-and-answer format is used by W. King Engel, who examines histochemical evidence in detail and honestly concludes that the 'site of the lesion' has not been located by these methods. A. G. Engel follows with an electron microscopical study in Duchenne dystrophy in which no consistent abnormalities were found in blood vessels in muscles, axons, endplates or mitochondria in endplates, but which showed membrane gaps in a small proportion of fibres, and interesting *in vivo* studies reveal that several substances, including enzymes, move through these gaps.

Although a large part of the book is concerned with Duchenne dystrophy there are also papers dealing with other diseases such as myotonia and periodic paralysis.

Muscle research is not latent and although much of the data in this book appeared in publications antedating the conference (sometimes by years) the availability of so much interrelated historical, technical and theoretical work in one volume will be of great value in many departments including those of neuropathology, neurology, genetics, pædiatrics, biochemistry and physiology.

DAVID DOYLE

Slow Virus Infections of the Central Nervous System. Edited by Volker ter Meulen and Michael Katz. 1977. Pp. 272. Berlin: Springer-Verlag. Price DM. 62.40.

Since this book is basically the proceedings of a workshop on slow virus infections of the nervous system held in the University of Wurzburg in March 1975, it may already seem rather out of date. Yet the chapters are useful reviews of the field at that time, and probably much of the work undertaken on slow virus diseases in the course of the last three years has been aimed at consolidating information about existing diseases rather than establishing new concepts. The editors should however have defined what they mean by slow virus infections of the nervous system, since many of the diseases referred to in the book would not immediately be classified as being in that group by me, but I am no virologist.

The book is presented in four parts. The first deals with 'unconventional agents', *viz.* those responsible for scrapie and the subacute spongiform encephalopathies, and the progressive pneumonia viruses of sheep. This is followed by a section on 'conventional agents', and includes reviews on progressive multifocal leukoencephalopathy and subacute sclerosing panencephalitis. There are also some observations on borna disease. The third part, need we say it, is devoted to multiple sclerosis and incorporates some facts and a considerable amount of speculation, while the fourth—interesting reading—is a 'critique on the investigational approaches to etiology and pathogenesis'.

I enjoyed reading this book, and it will be a useful source of references up to about 1974. But it does not really incorporate anything new or particularly stimulating.

HUME ADAMS

Handbook of Clinical Neurology. Edited by P. J. Vincken and G. W. Bruyn. Vol. 32. **Congenital Malformations of the Spine and Spinal Cord.** 1978. Pp. 600. Amsterdam: Elsevier/North Holland. Price Dfl. 235.00.

The neurologist will find himself on more familiar ground with this volume of the Handbook. From the lamented Djindjian's addendum to his authoritative review of spinal cord angiomas we learn that his chapter was written in 1974–75, and it is a pity that a brief note covers his subsequent experience of diagnosis and treatment in the field. By contrast, Brocklehurst, who was recruited late in the day, was able to provide an excellent, up-to-date account of spina bifida. The problem of timely publication affects all editors of compendia, and readers must look elsewhere for more recent developments in many of the topics covered by such works.

There are many excellent chapters in this volume. Salam and Adams contribute a comprehensive but enviably succinct account of the Arnold-Chiari malformation. Roaf's chapter on scoliosis and other spine malformations will prove useful to the medical neurologist. Wilkins and Odom provide complete lists of recorded examples of intrapelvic, lumbar and thoracic meningoceles up to 1971, plus a record of their own patients; this chapter has an evident value to the neurosurgeon. These cited contributions have been chosen at random, for there are several others which deserve equal mention.

In summary, medical and surgical neurologists will find the book a comprehensive work covering the literature thoroughly up to the presumed deadline afforded the contributors. It is recommended for all departmental libraries.

R. A. HENSON

Intercellular Junctions and Synapses. Receptors and Recognition. Series B, Volume 2. Edited by J. Feldman, N. B. Gilula and J. D. Pitts. 1978. Pp. 246. London: Chapman and Hall; New York: John Wiley. Price £15.00.

This book describes current research work aimed at establishing how neural cells communicate with each other. Although of only limited clinical interest this book provides up-to-date reviews of chemical synapses and gap junctions which will be of particular interest to neurologists and cell biologists.

D. M. BOWEN

FORTHCOMING EVENT

INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY

Noordwijkerhout, Netherlands, June 27–30 1979

For registration information, contact Dr. Dirk J. Bakker, Paedologisch Instituut, Koningslaan 22, 1075 AD Amsterdam, Holland.

For information regarding submission of papers and poster session contact Dr. Elizabeth Warrington, The National Hospital, Psychology Department, Queen Square, London WC1N 3BG.

BRAIN

A JOURNAL OF NEUROLOGY

Brain

A Journal of Neurology

Edited by C. G. PHILLIPS

Deputy Editor R. A. HENSON

with the help of

J. HUME ADAMS	R. W. GILLIATT	M. VOGT
A. N. DAVISON	E. C. HUTCHINSON	L. WEISKRANTZ

Assistant Editor E. MACDOUGALL

Secretary and Treasurer J. M. NEWSOM DAVIS

VOLUME CI

★

OXFORD
AT THE CLARENDON PRESS

1978

Oxford University Press, Walton Street, Oxford OX2 6DP
OXFORD LONDON GLASGOW
NEW YORK TORONTO MELBOURNE WELLINGTON
KUALA LUMPUR SINGAPORE JAKARTA HONG KONG TOKYO
DELHI BOMBAY CALCUTTA MADRAS KARACHI
NAIROBI DAR ES SALAAM CAPE TOWN

© *Oxford University Press 1978*

Printed in Great Britain
at the University Press, Oxford
by Eric Buckley
Printer to the University

CONTENTS

PAGE

The Gate Control Theory of Pain Mechanisms. P. D. Wall 1

Some Frequency Response Characteristics of Parkinsonism on Pursuit Tracking. Kenneth Flowers 19

Lack of Prediction in the Motor Behaviour of Parkinsonism. Kenneth Flowers .. 35

Carcinomatous Neuromuscular Syndromes. Thomas Paul, B. C. Katiyar, Surendra Misra and G. C. Pant 53

A Study of the Visual Defect in Verbal Alexia–Simultanagnosia. David N. Levine and Ronald Calvanio 65

Mental Phenomena Evoked by Electrical Stimulation of the Human Hippocampal Formation and Amygdala. Eric Halgren, Richard D. Walter, Diana G. Cherlow and Paul H. Crandall 83

Trigeminal False Localizing Signs and their Causation. J. E. A. O'Connell .. 119

Focal Contralateral Myoclonus Produced by Inhibition of Gaba Action in the Caudate Nucleus of Rats. D. Tarsy, C. J. Pycock, B. S. Meldrum and C. D. Marsden 143

Word-comprehension and Word-retrieval in Patients with Localized Cerebral Lesions. A. K. Coughlan and Elizabeth K. Warrington 163

Variations in Regional Cortical Blood Flow in the Right and Left Hemispheres during Automatic Speech. Bo Larsen, Erik Skinhøj and Niels A. Lassen .. 193

The Natural History of Intermittent Claudication of the Cauda Equina. J. N. Blau and Valentine Logue 211

A Critical Appraisal of Posterior Fossa Surgery for Communicating Syringomyelia. Bernard Williams 223

The Corticopontine Projection in the Rhesus Monkey. P. Brodal 251

Late Blink Reflex Changes in Lateral Medullary Lesions. B. W. Ongerboer de Visser and H. G. J. M. Kuypers 285

The Sensation of Heaviness after Surgical Disconnection of the Cerebral Hemispheres in Man. S. C. Gandevia 295

Somatosensory Epilepsy. F. Mauguiere and J. Courjon 307

Subacute Spongiform Encephalopathy (Creutzfeldt–Jakob Disease). C. L. Masters and E. P. Richardson, Jr. 333

PAGE

Acetylcholine Receptors and End-Plate Electrophysiology in Myasthenia Gravis. Y. Ito, R. Miledi, A. Vincent and J. Newsom-Davis 345

Bilateral Tactile Aphasia: A Tacto-verbal Dysfunction. Marie-France Beauvois, Brigitte Saillant, Vincent Meininger and François Lhermitte 381

The Neuroanatomy of Amnesia: A Critique of the Hippocampal Memory Hypothesis. James A. Horel 403

Electroencephalographic Studies of Myoclonus: Myoclonus-related Cortical Spikes and High Amplitude Somatosensory Evoked Potentials. Hiroshi Shibasaki, Yoriaki Yamashita and Yoshigoro Kuroiwa 447

Familial Myoclonic Epilepsy with Ataxia and Neuropathy with Additional Features of Friedreich's Ataxia and Peroneal Muscular Atrophy. N. J. Smith, M. L. E. Espir and W. B. Matthews 461

Sensory Action Potentials and Biopsy of the Sural Nerve in Neuropathy. F. Behse and F. Buchthal 473

Factors Influencing the Risk of Multiple Sclerosis Developing in Patients with Optic Neuritis. D. A. S. Compston, J. R. Batchelor, C. J. Earl and W. I. McDonald 495

The Intrinsic Connections of the Cortex of Area 4 of the Monkey. K. C. Gatter and T. P. S. Powell 513

An Electron Microscopic Study of the Termination of Intracortical Axons upon Betz Cells in Area 4 of the Monkey. K. C. Gatter, J. J. Sloper and T. P. S. Powell 543

Hemisphere Function and Binocular Depth Perception. G. Danta, R. C. Hilton and D. J. O'Boyle 569

A Clinical and Genetic Study of Spinal Muscular Atrophy of Adult Onset. John H. Pearn, Peter Hudgson and John N. Walton 591

The Role of Frontal and Parietal Cortex in Cognitive Processing. Betty Ann Brody and Karl H. Pribram 607

Long Latency Event-related Components of the Auditory Evoked Potential in Dementia. Douglas S. Goodin, Kenneth C. Squires and Arnold Starr .. . 635

Selective Blockade by Scopolamine of Synaptic Responses in Cat's Caudate Nucleus and its Modification by Lesions of the Substantia Nigra. R. Spehlmann, K. Norcross and E. J. Grimmer 649

Measurements of Visual Evoked Potentials in Parkinson's Disease. Ivan Bodis-Wollner and Melvin D. Yahr 661

The Concept of a Sensorimotor Cortex: Its Early History, with Especial Emphasis on Two Early Experimental Contributions by W. Bechterew. Alfred Meyer .. 673

PAGE
Epileptic Brain Damage: The Role of Systemic Factors that Modify Cerebral Energy Metabolism. G. Blennow, J. B. Brierley, B. S. Meldrum and B. K. Siesjö 687

Effect of Ethanol on Neuronal Activity in the Parietal Association Cortex of Alert Monkeys. J. Hyvärinen, M. Laakso, R. Roine, L. Leinonen and H. Sippel .. 701

Notices of Recent Publications 187, 369, 555, 717

INDEX
TO
BRAIN
A JOURNAL OF NEUROLOGY
FOR
VOL. CI, 1978

AUTHORS

PAGE

Batchelor, J. R., Compston, D. A. S., Earl, C. J. and McDonald, W. I.
(*See* **Compston, D. A. S.** *et al.*) 495

Beauvois, M.-F., Saillant, B., Meininger, V. and Lhermitte, F.
Bilateral Tactile Aphasia: A Tacto-verbal Dysfunction 381

Behse, F. and Buchthal, F.
Sensory Action Potentials and Biopsy of the Sural Nerve in Neuropathy .. 473

Blau, J. N. and Logue, V.
The Natural History of Intermittent Claudication of the Cauda Equina .. 211

Blennow, G., Brierley, J. B., Meldrum, B. S. and Siesjö, B. K.
Epileptic Brain Damage: The Role of Systemic Factors that Modify Cerebral Energy Metabolism 687

Bodis-Wollner, I. and Yahr, M. D.
Measurements of Visual Evoked Potentials in Parkinson's Disease 661

Brierley, J. B., Blennow, G., Meldrum, B. S. and Siesjö, B. K.
(*See* **Blennow, G.** *et al.*) 687

Brodal, P.
The Corticopontine Projection in the Rhesus Monkey 251

Brody, B. A. and Pribram, K. H.
The Role of Frontal and Parietal Cortex in Cognitive Processing: Tests of Spatial and Sequence Functions 607

Buchthal, F. and Behse, F.
(*See* **Behse, F. and Buchthal, F.**) 473

PAGE

Calvanio, R. and Levine, D. N.
(*See* **Levine, D. N. and Calvanio, R.**) 65

Cherlow, D. G., Halgren, E., Walter, R. D. and Crandall, P. H.
(*See* **Halgren, E.** *et al.*) 83

Compston, D. A. S., Batchelor, J. R., Earl, C. J. and McDonald, W. I.
Factors Influencing the Risk of Multiple Sclerosis Developing in Patients with Optic Neuritis 495

Coughlan, A. K. and Warrington, E. K.
Word-comprehension and Word-retrieval in Patients with Localized Cerebral Lesions 163

Courjon, J. and Mauguiere, F.
(*See* **Mauguiere, F. and Courjon, J.**) 307

Crandall, P. H., Halgren, E., Walter, R. D. and Cherlow, D. G.
(*See* **Halgren, E.** *et al.*) 83

Danta, G., Hilton, R. C. and O'Boyle, D. J.
Hemisphere Function and Binocular Depth Perception 569

Earl, C. J., Compston, D. A. S., Batchelor, J. R. and McDonald, W. I.
(*See* **Compston, D. A. S.** *et al.*) 495

Espir, M. L. E., Smith, N. J. and Matthews, W. B.
(*See* **Smith, N. J.** *et al.*) 461

Flowers, K.
Some Frequency Response Characteristics of Parkinsonism on Pursuit Tracking 19
Lack of Prediction in the Motor Behaviour of Parkinsonism 35

Gandevia, S. C.
The Sensation of Heaviness after Surgical Disconnection of the Cerebral Hemispheres in Man 295

Gatter, K. C. and Powell, T. P. S.
The Intrinsic Connections of the Cortex of Area 4 of the Monkey 513

Gatter, K. C., Sloper, J. J. and Powell, T. P. S.
An Electron Microscopic Study of the Termination of Intracortical Axons upon Betz Cells in Area 4 of the Monkey 543

Goodin, D. S., Squires, K. C. and Starr, A.
Long Latency Event-related Components of the Auditory Evoked Potential in Dementia 635

Grimmer, E. J., Spehlmann, R. and Norcross, K.
(*See* **Spehlmann, R.** *et al.*) 649

PAGE

Halgren, E., Walter, R. D., Cherlow, D. G. and Crandall, P. H.
Mental Phenomena Evoked by Electrical Stimulation of the Human Hippocampal Formation and Amygdala 83

Hilton, R. C., Danta, G. and O'Boyle, D. J.
(*See* **Danta, G.** *et al.*) 569

Horel, J. A.
The Neuroanatomy of Amnesia: A Critique of the Hippocampal Memory Hypothesis 403

Hudgson, P., Pearn, J. H. and Walton, J. N.
(*See* **Pearn, J. H.** *et al.*) 591

Hyvärinen, J., Laakso, M., Roine, R., Leinonen, L. and Sippel, H.
Effect of Ethanol on Neuronal Activity in the Parietal Association Cortex of Alert Monkeys 701

Ito, Y., Miledi, R., Vincent, A. and Newsom-Davis, J.
Acetylcholine Receptors and End-plate Electrophysiology in Myasthenia Gravis 345

Katiyar, B. C., Paul, T., Misra, S. and Pant, G. C.
(*See* **Paul, T.** *et al.*) 53

Kuroiwa, Y., Shibasaki, H. and Yamashita, Y.
(*See* **Shibasaki, H.** *et al.*) 447

Kuypers, H. G. J. M. and Ongerboer de Visser, B. W.
(*See* **Ongerboer de Visser, B. W. and Kuypers, H. G. J. M.**) 285

Laakso, M., Hyvärinen, J., Roine, R., Leinonen, L. and Sippel, H.
(*See* **Hyvärinen, J.** *et al.*) 701

Larsen, B., Skinhøj, E. and Lassen, N. A.
Variations in Regional Cortical Blood Flow in the Right and Left Hemispheres during Automatic Speech 193

Lassen, N. A., Larsen, B. and Skinhøj, E.
(*See* **Larsen, B.** *et al.*) 193

Leinonen, L., Hyvärinen, J., Laakso, M., Roine, R. and Sippel, H.
(*See* **Hyvärinen, J.** *et al.*) 701

Lhermitte, F., Beauvois, M.-F., Saillant, B. and Meininger, V.
(*See* **Beauvois, M.-F.** *et al.*) 381

Logue, V. and Blau, J. N.
(*See* **Blau, J. N. and Logue, V.**) 211

McDonald, W. I., Compston, D. A. S., Batchelor, J. R. and Earl, C. J.
(*See* **Compston, D. A. S.** *et al.*) 495

PAGE

Marsden, C. D., Tarsy, D., Pycock, C. J. and Meldrum, B. S.
(*See* **Tarsy, D.** *et al.*) 143

Masters, C. L. and Richardson, E. P., Jr.
Subacute Spongiform Encephalopathy (Creutzfeldt–Jakob Disease) 333

Matthews, W. B., Smith, N. J. and Espir, M. L. E.
(*See* **Smith, N. J.** *et al.*) 461

Mauguiere, F. and Courjon, J.
Somatosensory Epilepsy 307

Meininger, V., Beauvois, M.-F., Saillant, B. and Lhermitte, F.
(*See* **Beauvois, M.-F.** *et al.*) 381

Levine, D. N. and Calvanio, R.
A Study of the Visual Defect in Verbal Alexia–Simultanagnosia 65

Meldrum, B. S., Blennow, G., Brierley, J. B. and Siesjö, B. K.
(*See* **Blennow, G.** *et al.*) 687

Meldrum, B. S., Tarsy, D., Pycock, C. J. and Marsden, C. D.
(*See* **Tarsy, D.** *et al.*) 143

Meyer, A.
The Concept of a Sensorimotor Cortex: Its Early History, with Especial Emphasis on Two Early Experimental Contributions by W. Bechterew . . 673

Miledi, R., Ito, Y., Vincent, A. and Newsom-Davis, J.
(*See* **Ito, Y.** *et al.*) 345

Misra, S., Paul, T., Katiyar, B. C. and Pant, G. C.
(*See* **Paul, T.** *et al.*) 53

Newsom-Davis, J., Ito, Y., Miledi, R. and Vincent, A.
(*See* **Ito, Y.** *et al.*) 345

Norcross, K., Spehlmann, R. and Grimmer, E. J.
(*See* **Spehlmann, R.** *et al.*) 649

O'Boyle, D. J., Danta, G. and Hilton, R. C.
(*See* **Danta, G.** *et al.*) 569

O'Connell, J. E. A.
Trigeminal False Localizing Signs and their Causation 119

Ongerboer de Visser, B. W. and Kuypers, H. G. J. M.
Late Blink Reflex Changes in Lateral Medullary Lesions 285

Pant, G. C., Paul, T., Katiyar, B. C. and Misra, S.
(*See* **Paul, T.** *et al.*) 53

Paul, T., Katiyar, B. C., Misra, S. and Pant, G. C.
Carcinomatous Neuromuscular Syndromes 53

PAGE

Pearn, J. H., Hudgson, P. and Walton, J. N.
A Clinical and Genetic Study of Spinal Muscular Atrophy of Adult Onset: The Autosomal Recessive Form as a Discrete Disease Entity 591

Powell, T. P. S. and Gatter, K. C.
(*See* **Gatter, K. C. and Powell, T. P. S.**) 513

Powell, T. P. S., Gatter, K. C. and Sloper, J. J.
(*See* **Gatter, K. C.** *et al.*) 543

Pribram, K. H. and Brody, B. A.
(*See* **Brody, B. A. and Pribram, K. H.**) 607

Pycock, C. J., Tarsy, D., Meldrum, B. S. and Marsden, C. D.
(*See* **Tarsy, D.** *et al.*) 143

Richardson, E. P., Jr. and Masters, C. L.
(*See* **Masters, C. L. and Richardson, E. P., Jr.**) 333

Roine, R., Hyvärinen, J., Laakso, M., Leinonen, L. and Sippel, H.
(*See* **Hyvärinen, J.** *et al.*) 701

Saillant, B., Beauvois, M.-F., Meininger, V. and Lhermitte, F.
(*See* **Beauvois, M.-F.** *et al.*) 381

Shibasaki, H., Yamashita, Y. and Kuroiwa, Y.
Electroencephalographic Studies of Myoclonus: Myoclonus-related Cortical Spikes and High Amplitude Somatosensory Evoked Potentials 447

Siesjö, B. K., Blennow, G., Brierley, J. B. and Meldrum, B. S.
(*See* **Blennow, G.** *et al.*) 687

Sippel, H., Hyvärinen, J., Laakso, M., Roine, R. and Leinonen, L.
(*See* **Hyvärinen, J.** *et al.*) 701

Skinhøj, E., Larsen, B. and Lassen, N. A.
(*See* **Larsen, B.** *et al.*) 193

Sloper, J. J., Gatter, K. C. and Powell, T. P. S.
(*See* **Gatter, K. C.** *et al.*) 543

Smith, N. J., Espir, M. L. E. and Matthews, W. B.
Familial Myoclonic Epilepsy with Ataxia and Neuropathy with Additional Features of Friedreich's Ataxia and Peroneal Muscular Atrophy 461

Spehlmann, R., Norcross, K. and Grimmer, E. J.
Selective Blockade by Scopolamine of Synaptic Responses in Cat's Caudate Nucleus and its Modification by Lesions of the Substantia Nigra 649

Squires, K. C., Goodin, D. S. and Starr, A.
(*See* **Goodin, D. S.** *et al.*) 635

PAGE

Starr, A., Goodin, D. S. and Squires, K. C.
(*See* **Goodin, D. S.** *et al.*) 635

Tarsy, D., Pycock, C. J., Meldrum, B. S. and Marsden, C. D.
Focal Contralateral Myoclonus Produced by Inhibition of Gaba Action in the Caudate Nucleus of Rats 143

Vincent, A., Ito, Y., Miledi, R. and Newsom-Davis, J.
(*See* **Ito, Y.** *et al.*) 345

Wall, P. D.
The Gate Control Theory of Pain Mechanisms 1

Walter, R. D., Halgren, E., Cherlow, D. G. and Crandall, P. H.
(*See* **Halgren, E.** *et al.*) 83

Walton, J. N., Pearn, J. H. and Hudgson, P.
(*See* **Pearn, J. H.** *et al.*) 591

Warrington, E. K. and Coughlan, A. K.
(*See* **Coughlan, A. K. and Warrington, E. K.**) 163

Williams, B.
A Critical Appraisal of Posterior Fossa Surgery for Communicating Syringomyelia 223

Yahr, M. D. and Bodis-Wollner, I.
(*See* **Bodis-Wollner, I. and Yahr, M. D.**) 661

Yamashita, Y., Shibasaki, H. and Kuroiwa, Y.
(*See* **Shibasaki, H.** *et al.*) 447

SUBJECTS

PAGE

Alexia—Simultanagnosia, Verbal, A Study of the Visual Defect in. D. N. Levine and R. Calvanio 65

Amnesia, The Neuroanatomy of: Critique of Hippocampal Memory Hypothesis. J. A. Horel 403

Aphasia, Bilateral Tactile: A Tacto-verbal Dysfunction. M.-F. Beauvois, B. Saillant, V. Meininger and F. Lhermitte 381

Area 4 of Monkey, Electron Microscopic Study of Termination of Intracortical Axons upon. K. C. Gatter, J. J. Sloper and T. P. S. Powell 543

Axons, Intracortical, Electron Microscopic Study of Termination upon Betz Cells in Area 4 of Monkey. K. C. Gatter, J. J. Sloper and T. P. S. Powell 543

Betz Cells in Area 4 of Monkey, Electron Microscopic Study of Termination of Intracortical Axons upon. K. C. Gatter, J. J. Sloper and T. P. S. Powell .. 543

Blink Reflex, Late, Changes in Lateral Medullary Lesions. B. W. Ongerboer de Visser and H. G. J. M. Kuypers 285

Brain Damage, Epileptic. The Role of Systemic Factors that Modify Cerebral Energy Metabolism. G. Blennow, J. B. Brierley, B. S. Meldrum and B. K. Siesjö 687

Carcinomatous Neuromuscular Syndromes. T. Paul, B. C. Katiyar, S. Misra and G. C. Pant 53

Cauda Equina, Natural History of Intermittent Claudication of. J. N. Blau and V. Logue 211

Caudate Nucleus, Cat's, Synaptic Responses in, Selective Blockade by Scopolamine of, and its Modification by Lesions of the Substantia Nigra. R. Spehlmann, K. Norcross and E. J. Grimmer 649

Caudate Nucleus, Rats, Focal Contralateral Myoclonus Produced by Inhibition of GABA Action in. D. Tarsy, C. J. Pycock, B. S. Meldrum and C. D. Marsden 143

Cerebral Lesions, Localized, Word-comprehension and Word-retrieval in Patients with. A. K. Coughlan and E. K. Warrington 163

Cognitive Processing, Role of Frontal and Parietal Cortex in: Tests of Spatial and Sequence Functions. B. A. Brody and K. H. Pribram 607

Cortex, Frontal and Parietal, Role in Cognitive Processing: Tests of Spatial and Sequence Functions. B. A. Brody and K. H. Pribram 607

PAGE

Cortex of Area 4 of Monkey, Intrinsic Connections of. K. C. Gatter and T. P. S. Powell 513

Cortex, Sensorimotor, Concept of: Its Early History, with Especial Emphasis on Two Early Experimental Contributions by W. Bechterew. A. Meyer 673

Cortical Blood Flow, Regional, Variations in, in Right and Left Hemispheres during Automatic Speech. B. Larsen, E. Skinhøj and N. A. Lassen 193

Corticopontine Projection in the Rhesus Monkey. P. Brodal 251

Creutzfeldt-Jakob Disease (Subacute Spongiform Encephalopathy). C. L. Masters and E. P. Richardson, Jr. 333

Dementia, Auditory Evoked Potential in, Long Latency Event-related Components of. D. S. Goodin, K. C. Squires and A. Starr 635

Depth Perception, Binocular, Hemisphere Function and. G. Danta, R. C. Hilton and D. J. O'Boyle 569

Electrical Stimulation of Human Hippocampal Formation and Amygdala, Mental Phenomena Evoked by. E. Halgren, R. D. Walter, D. G. Cherlow and P. H. Crandall 83

Epilepsy, Familial Myoclonic, with Ataxia and Neuropathy, with Additional Features of Friedreich's Ataxia and Peroneal Muscular Atrophy. N. J. Smith, M. L. E. Espir and W. B. Matthews 461

Epilepsy, Somatosensory. F. Mauguiere and J. Courjon 307

Epileptic Brain Damage: Role of Systemic Factors that Modify Cerebral Energy Metabolism. G. Blennow, J. B. Brierley, B. S. Meldrum and B. K. Siesjö .. 687

Ethanol, Effect on Neuronal Activity of, in Parietal Association Cortex of Alert Monkeys. J. Hyvärinen, M. Laakso, R. Roine, L. Leinonen and H. Sippel .. 701

Evoked Potential, Auditory, in Dementia, Long Latency Event-related Components of. D. S. Goodin, K. C. Squires and A. Starr 635

Evoked Potentials, Visual, Measurements in Parkinson's Disease. I. Bodis-Wollner and M. D. Yahr 661

Friedreich's Ataxia and Peroneal Muscular Atrophy, Familial Myoclonic Epilepsy with Ataxia and Neuropathy with Additional Features of. N. J. Smith, M. L. E. Espir and W. B. Matthews 461

Gate Control Theory of Pain Mechanisms. P. D. Wall 1

Heaviness, Sensation of, after Surgical Disconnection of Cerebral Hemispheres in Man. S. C. Gandevia 295

Hemisphere Function and Binocular Depth Perception. G. Danta, R. C. Hilton and D. J. O'Boyle 569

PAGE

Hemispheres, Cerebral, in Man, Surgical Disconnection of, Sensation of Heaviness after. S. C. Gandevia 295

Hemispheres, Right and Left, Variations in Regional Cortical Blood Flow during Automatic Speech. B. Larsen, E. Skinhøj and N. A. Lassen 193

Hippocampal Formation and Amygdala, Human, Mental Phenomena Evoked by Electrical Stimulation of. E. Halgren, R. D. Walter, D. G. Cherlow and P. H. Crandall 83

Hippocampal Memory Hypothesis, Critique of: the Neuroanatomy of Amnesia. J. A. Horel 403

Intermittent Claudication of Cauda Equina, Natural History of. J. N. Blau and V. Logue 211

Lateral Medullary Lesions, Late Blink Reflex Changes in. B. W. Ongerboer de Visser and H. G. J. M. Kuypers 285

Mental Phenomena Evoked by Electrical Stimulation of Human Hippocampal Formation and Amygdala. E. Halgren, R. D. Walter, D. G. Cherlow and P. H. Crandall 83

Multiple Sclerosis Developing in Patients with Optic Neuritis, Factors Influencing Risk of. D. A. S. Compston, J. R. Batchelor, C. J. Earl and W. I. McDonald 495

Muscular Atrophy, Peroneal, Familial Myoclonic Epilepsy with Ataxia and Neuropathy with Additional Features of Friedreich's Ataxia and. N. J. Smith, M. L. E. Espir and W. B. Matthews 461

Muscular Atrophy of Adult Onset, Spinal, a Clinical and Genetic Study of: The Autosomal Recessive Form as a Discrete Disease Entity. J. H. Pearn, P. Hudgson and J. N. Walton 591

Myasthenia Gravis, Acetylcholine Receptors and End-plate Electrophysiology in. Y. Ito, R. Miledi, A. Vincent and J. Newsom-Davis 345

Myoclonus, Electroencephalographic Studies of: Myoclonus-related Cortical Spikes and High Amplitude Somatosensory Evoked Potentials. H. Shibasaki, Y. Yamashita and Y. Kuroiwa 447

Myoclonus, Focal Contralateral, Produced by Inhibition of GABA Action in Caudate Nucleus of Rats. D. Tarsy, C. J. Pycock, B. S. Meldrum and C. D. Marsden 143

Neuritis, Optic, Factors Influencing Risk of Multiple Sclerosis Developing in Patients with. D. A. S. Compston, J. R. Batchelor, C. J. Earl and W. I. McDonald .. 495

Neuropathy, Sensory Action Potentials and Biopsy of the Sural Nerve in. F. Behse and F. Buchthal 473

Pain Mechanisms, Gate Control Theory of. P. D. Wall 1

PAGE

Parietal Association Cortex of Alert Monkeys, Effect of Ethanol on Neuronal Activity of. J. Hyvärinen, M. Laakso, R. Roine, L. Leinonen and H. Sippel . . 701

Parkinson's Disease, Measurements of Visual Evoked Potentials in. I. Bodis-Wollner and M. D. Yahr 661

Parkinsonism, Motor Behaviour of, Lack of Prediction in. K. Flowers 35

Parkinsonism, Some Frequency Response Characteristics of, on Pursuit Tracking. K. Flowers 19

Perception, Binocular Depth, Hemisphere Function and. G. Danta, R. C. Hilton and D. J. O'Boyle 569

Posterior Fossa Surgery for Communicating Syringomyelia, A Critical Appraisal of. B. Williams 223

Scopolamine, Selective Blockade of Synaptic Responses in Cat's Caudate Nucleus and its Modification by Lesions of the Substantia Nigra by. R. Spehlmann, K. Norcross and E. J. Grimmer 649

Sensory Action Potentials and Biopsy of the Sural Nerve in Neuropathy. F. Behse and F. Buchthal 473

Speech, Automatic, Variations in Regional Cortical Blood Flow in Right and Left Hemispheres during. B. Larsen, E. Skinhøj and N. A. Lassen 193

Subacute Spongiform Encephalopathy (Creutzfeldt-Jakob Disease). C. L. Masters and E. P. Richardson, Jr. 333

Substantia Nigra, Lesions of, Selective Blockade by Scopolamine of Synaptic Responses in Cat's Caudate Nucleus and its Modification by. R. Spehlmann, K. Norcross and E. J. Grimmer 649

Syringomyelia, Communicating, Posterior Fossa Surgery for, A Critical Appraisal. B. Williams 223

Tactile Aphasia, Bilateral: A Tacto-verbal Dysfunction. M.-F. Beauvois, B. Saillant, V. Meininger and F. Lhermitte 381

Trigeminal False Localizing Signs and their Causation. J. E. A. O'Connell 119

Visual Defect in Verbal Alexia—Simultanagnosia, A Study of. D. N. Levine and R. Calvanio 65

Word-comprehension and Word-retrieval in Patients with Localized Cerebral Lesions. A. K. Coughlan and E. K. Warrington 163